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HENRY ASBURY CHRISTIAN

HENRY ASBURY CHRISTIAN died of a coronary thrombosis on Aug. 24, 1951, at Whitefield, N. H., in his seventy-fifth year.

During the first one-half of this century, Henry Christian exerted a great influence on medical teaching in North America. He had been brought up, so to speak, in the tradition of pathological anatomy. In fact, he progressed from the Department of Pathology at the Boston City Hospital to the chair of Medicine at Harvard Medical School in 1908 and eventually became Physician-in-Chief of Peter Bent Brigham Hospital. This period was the beginning of what might with justice be called the era of house cleaning of medical schools and medical education in the United States, and Henry Christian was prominent in the crusade. Under the leadership of Christian, Cushing, Cannon, Wolbach, Zinsser, and many others, an impetus was given to medical teaching and research which was felt all over the country and, indeed, throughout the world, with an ever increasing tempo.

Henry Christian held the chair of Medicine at Harvard from 1908 to 1939. Thus, thirty-one separate classes of Harvard medical students and innumerable postgraduates were privileged to sit at the feet of the master and benefit from his wisdom, sound teaching, and sympathetic understanding. It is hoped that some more facile pen, guided by the heart and mind of one who enjoyed these rare presents, will write more fully of Henry Christian as a man, a physician, and a teacher. I am sure that those to whom he was one or all of these would wish to join us in expressing deepest sympathy to Mrs. Christian in her great loss which is shared by a host of students and colleagues, however remotely they knew him.

On August 24, there was received the following letter accompanied by the manuscript. They are published without any change of the original. The Editor assumed the privilege of correcting the galley proof as a last tribute to a great man.

EDITOR

MOUNTAIN VIEW HOUSE
WHITEFIELD, NEW HAMPSHIRE

Aug. 16, 1951

Dear Dr. Mackie,

Here is a paper I am offering for publication in the Am. Jour. of Heart Diseases. I had a paper in the first volume so this may be in the form of a review done from my 25 years of retirement from active work.

With cordial greetings

Sincerely

Henry Christian

NEARLY TEN DECADES OF INTEREST IN IDIOPATHIC PERICARDITIS

HENRY A. CHRISTIAN, M.D.

BOSTON, MASS.

MORE than fifty years ago, actually while a student in the Johns Hopkins Medical School in 1898 to 1900 under Dr. Osler, I came to know of idiopathic or primary pericarditis, for I had read of it in Osler's *Principles and Practice of Medicine*[1] in the second edition published in 1895. There I found written the following: "Primary, so-called idiopathic, inflammation of this membrane is rare, but cases are met with, most commonly in children, in which there is no evidence of rheumatism or other condition with which the disease is usually associated." This is essentially what had appeared in the first edition of 1892 and was continued with but little variation through the next eleven editions. This term, idiopathic pericarditis, had had a frequent usage in earlier medical literature. In the first series of the index catalogue of the Surgeon General's Office in Washington, D.C., in the volume published in 1889, the term appears in the title of some dozen papers[2] going back as far as 1854. Curiously enough, in the second series, published in 1907, it appears only once[2a] and in the third series not at all.

In the spring of 1909, on May 21, 1909, in one of the first series of lectures given by me to students of the Harvard Medical School after being appointed Hersey Professor of the Theory and Practice of Physic, I said,[3] "Now as far as pericarditis is concerned, you can get a primary pericarditis, primary in the sense that you have no other inflammatory process in the body, you have no particular portal of entry that you can demonstrate, and so far as you can see, the primary condition, the sole condition, is an inflammation of the pericardium. These cases are comparatively rare. Now you find in a good many text books [such as those of Allbutt, Edwards, Loomis and Thompson, von Mehring, Osler, Osler and McCrae, Thompson, Strümpell, Twentieth Century Practice, Tyson, Wood, and Fitz] the term, idiopathic pericarditis, used. That simply means that it is an infection the cause of which is not known. In a certain number of these cases when they come to autopsy, if you make cultures from the pericardium, you find no bacteria; that is probably the case also with many cases of infection of the pericardium associated with rheumatism. However, the word, idiopathic, probably is not justified. It simply means that the exact cause is not known. Yet there is reason to believe that they are true bacterial infections, but that the organisms have died out or are of a type not easily cultivated on our medium, or that they have very slight viability, and you do not demonstrate them, though probably they are present. So far as classification is concerned, it is not necessary to have a group of idiopathic cases." Now, forty-two years later, were I giving

this lecture, I probably would add to the next to the last sentence: "Very possibly, under the conditions cited, the cause is a virus."

Writing in 1927 for my book, entitled *The Diagnosis and Treatment of Diseases of the Heart*, which was published by the Oxford University Press in 1928, I said of the idiopathic type, "There is a type of acute pericarditis which for a better name may be called idiopathic. There are no signs of rheumatism antecedent to, or accompanying, the pericarditis. There is no evidence of other inflammatory process to cause the pericarditis either by extension or metastasis. There is no underlying chronic disease. In its various clinical phenomena it is more like the rheumatic type than any other, except there is no suggestion of any of the symptoms and signs of acute rheumatic fever. However, unless the pericarditis represents the sole disturbance caused by the rheumatic organism, it cannot be called rheumatic. In this group prognosis is very good. As this group constitutes a fairly distinct clinical entity, it seems well to separate these cases under the term, idiopathic."

Diagnosis of idiopathic pericarditis usually is easy, if the heart is listened to, for then there will be found almost always and soon the characteristic to-and-fro pericardial rub, search for which has been suggested by the pain or discomfort in the cardiac region or the upper one-half of the abdomen. The differential diagnosis from myocardial infarction has been a concern recently of numerous discussers of this form of acute pericarditis.[7-11] However, rarely is there any real difficulty, since, when either one is causative of symptoms, the difference in them, especially in the pain, its radiation, and the causes of its exacerbation, almost always is diagnostic of the existing condition in the heart even without electrocardiograms. Actually, diagnosis from myocardial infarction appears to have caused more discussion of diagnosis than any other feature of the recently published reports. However, both of these conditions are ones that I found that my clinical clerks (senior students in the medical school), after history taking and physical examination, misdiagnosed very infrequently indeed when they reported their patient on ward rounds the morning following the patient's admission and before any electrocardiogram had been studied.

Treatment equally is easy, for nothing more seems needed for most patients other than the management of the discomfort by general and local measures and a brief period of bed rest, since these patients recover soon and subsequently appear to show no evidence of cardiac lesion or cardiac disability, certainly none in the few years following the acute attack, even if there has been a repetition of this, as is not infrequent. In more uncomfortable or recurring cases an antibiotic, as described in a later paragraph, should be used. There is the possibility, however, that long after the acute attack, symptoms and signs of constrictive pericarditis may have come. However, in the past history of the latter only rarely has there been the clear suggestion of an antecedent mild and brief acute pericarditis.

In a very few patients with this form of pericarditis, death has been reported, as in the case of McCord and Taguchi.[27] By some writers the term, latent pericarditis, has been given to these.[1,4a] The mechanism of death in such patients is not clear, since, as a rule, the amount of fluid in the pericardium has not seemed great enough to cause fatal cardiac tamponade, although this explanation has been

offered. At times death has occurred very quickly, and the diagnosis of pericarditis has been made only on post-mortem examination. When only fibrinous pericarditis has been found, it is difficult to understand how this could be responsible for death and especially for almost sudden death. Curiously, in some of the older papers for this last-mentioned condition the term, latent pericarditis, has appeared in the title of the paper.[4a] A fatal, "latent" pericarditis would seem an anomalous use of our language.

My own particular interest in these patients was derived from the not infrequent occurrence in them of upper abdominal pain, which easily might be, and sometimes was, mistaken for an acute abdominal condition requiring surgery. Some of these patients actually had their abdomens explored before the pericardial friction rub was heard, which, had it been heard earlier, would have diverted the surgeon from his inherent trend toward opening the abdomen. It should be impressed on the surgeon the great importance of listening over the heart for a rub in all patients with what so ineptly and etymologically crudely has been called the acute surgical abdomen.

This latter interest I expressed in the book of 1928[4b] as follows: "Particularly confusing in diagnosis is this pain of pericarditis referred to the upper abdomen and accompanied, as it sometimes may be, by abdominal tenderness, muscle spasm, nausea, and vomiting. Surgeons are apt to see these patients in the belief that some acute abdominal condition exists requiring prompt operation. For the surgeon, for whom, from lack of practice, the art of auscultation has atrophied, diagnostic error may lead to an unneeded operation. The idiopathic type of acute pericarditis is particularly prone to be diagnosed as an acute abdominal emergency, if pain is referred to the abdomen, for there is no antecedent or accompanying pain in the joints to suggest a rheumatic process, and the onset may be abrupt in a previously well individual. Some patients with such abdominal pain and the physical signs of pericarditis are undoubted cases of cardiac infarction, but probably not all of them." Obviously, the preceding words refer to any type of acute pericarditis, not alone to the idiopathic type.

Another finding in these patients interested me.[4c] That was a slight to marked dullness in the left side of the back in an area which, when small, would be at the angle of the left scapula and, when larger, would occupy the lower one-third to one-half of the left side of the back. Very rarely would this dullness extend into the axillary region. Often over the dull area there would be bronchial breathing of varying intensity, sometimes bronchophony. As a rule, râles were absent. I found these physical signs in thirty-nine of fifty-three consecutive patients with acute fibrinous pericarditis, which seemed to have been of rheumatic etiology in seventeen, while it appeared to be idiopathic in twenty-two. These findings were interpreted as pulmonary compression signs. The names, Bamberger's sign or Ewart's sign, have been used for these physical signs.

Difference of opinion among the observers of patients with acute idiopathic pericarditis exists as to whether the incident cardiac enlargement is due mainly to the presence of pericardial fluid or of dilatation, the larger number adhering to the second view. However, pericardial tap has not been infrequent in these patients, usually with the finding of fluid, sometimes blood-tinged or actually

bloody. The frequent demonstration of a positive Ewart's (Bamberger's) sign, as pointed out in the preceding paragraph, also is consistent with fluid in the pericardium, particularly in its posterior part, large enough to cause pressure on the left lower lobe of the lung with atelectasis causative of a positive Ewart's sign.

If there was dilatation enough to cause considerable cardiac enlargement, there should be more evidence than is usual in these patients of myocardial insufficiency and more patients with an arrhythmia. In idiopathic pericarditis the electrocardiogram infrequently shows the lengthened P-R interval, so commonly found in rheumatic heart disease, and arrhythmias are infrequent. Furthermore, in my experience,[4d] when heart block develops in a patient with acute pericarditis, as it not infrequently does, it is in those patients with definite symptoms and signs of rheumatic fever antedating the appearance of the pericardial friction rub, i.e., in rheumatic, not idiopathic, pericarditis. In my own patients with idiopathic pericarditis I never observed the development of heart block.

With changes in the myocardium extensive enough to cause dilatation of the heart, one would expect more evidences than are found of a residual myocarditis and more signs of a persisting or recurring myocardial insufficiency. All in all, it seems to me that cardiac enlargement in this form of pericarditis usually is caused by the presence of pericardial fluid rather than of myocardial lesions.

In the almost consuming interest in recent years of the cardiologists in cardiac infarction and electrocardiography, that phase of this form of pericarditis has taken a predominance in published papers, although to a noncardiologist that incorrect diagnosis has not seemed of much importance, since the differential diagnosis usually is easy and, if not made, no harm will come to the patient comparable to his having undergone an unneeded and serious surgical operation when the mistaken diagnosis has been of an acute intra-abdominal inflammatory lesion.

Since my use of the term, idiopathic pericarditis, other writers, apparently unfamiliar with the very frequent previous use of the term idiopathic since they make no reference to it, have used a differing terminology. In 1933, Bing[5] used the term, epidemic; in 1934, Willius[6] spoke of acute serofibrinous pericarditis secondary to pharyngitis, while in 1942 Barnes and Burchell,[7] in 1944 Wolff,[8] in 1946 Nay and Boyer[9] and Smalley and Ruddock,[10] and in 1947 Massey[11] seem to have refrained from naming in a specific way the type of pericarditis which they discussed, although from the descriptions all were dealing with cases at least some of which were of the type I had called idiopathic. Most of these latter authors,[7-11] as their titles show, were concerned chiefly with the simulation of acute pericarditis to coronary occlusion or myocardial infarction.

In 1947, Burchell[12] used the term acute nonspecific pericarditis and Cossio and Berconsky[13] the term aguda benigna. In 1948, Logue and Wendkos[14] called it acute pericarditis of benign type, while in 1949 Sease and Beckwith[15] named it acute nonspecific pericarditis and Beresford[16] fugitive pericarditis. In 1950, Levy and Patterson[17] wrote of it as of undetermined cause, while Feder and associates[18] made use of the term acute primary pericarditis, Evans[19] and Taubenhaus and Brams[20] of acute nonspecific benign pericarditis, Porter and associates[21] of nonspecific benign pericarditis, Pohl[22] of nonspecific or cryptic etiology, and McCord and Taguchi[27] of nonspecific pericarditis. In 1951, Carmichael and

associates[21] used the term acute nonspecific pericarditis and Brown[26] and Rosenow and Cross[28] acute benign pericarditis. In his 1947 paper Burchell[12] among other "diagnostic phrases" included in quotations acute, idiopathic, and primary idiopathic, without saying who previously had used these names.

These several papers leave with us for a choice of name the following terms: idiopathic, epidemic, primary, nonspecific, nonrheumatic, benign, relapsing, cryptic, fugitive, of undetermined cause, or a disease it has simulated, most often myocardial infarction or coronary occlusion. What we call it probably is of small import, although it seems undesirable not to have agreed on a single name. I suggest that idiopathic be used since it seems that was the name with which first it was baptized, since it is completely noncommittal as to the etiology of the condition, since it is, like the other suggested terms, a very simple word, and since it is the name which I had used both in 1909 and 1927.

Perusal of the various papers, especially the recent ones discussing it, has given us knowledge of the many parts of the body to which radiation of pain can take place, of the varieties of pain and the variations in its severity and duration, of the leucocyte count, the sedimentation rate, and the electrocardiographic pattern, all of which occur, as would be expected, in any of the types of acute pericarditis.

So far no one seems to have found out what the specific etiology of this type of pericarditis is, but an allergenic cause has been claimed.[24,25] To be expected next will be more reports of the effect on it of antibiotics, beyond the claimed good results from streptomycin in three of the patients studied by Porter, Clark, and Porter[21] and from penicillin in seven of eight cases studied by Evans[19] and the reported effective use of aureomycin by Taubenhaus and Brams[20] and Rosenow and Cross[28] and of terramycin by Rosenow and Cross.[28] Since this form of acute pericarditis is not of infrequent incidence, more such reports should be forthcoming. Since most of these patients recover without any specific therapy, there still may remain some uncertainty as to the specific effect of the antibiotics which have been used.

Also it is reasonable to expect before very long studies on etiology which will make use of such modern methods of study of the pericardial fluid as the application of our many available cultural methods including use of the embryonated egg, inoculation of various laboratory animals, and the application of immunological methods to the body fluids of the patient, some of which may be expected to reveal eventually the true cause of this form of pericarditis and enable us to give to it a name based on its etiology. As studies so far made of the pericardial fluid, unfortunately not very numerous, have failed to show a bacterial cause, there is good probability that some virus is causative, and this is suggested somewhat by its not infrequent sequence to the common cold and respiratory tract infections, which so often now are regarded as forms of virus disease.

SUMMARY

The clinical story of idiopathic pericarditis in its development over a period of nearly ten decades has been traced. In the earliest papers it was so well described

that surprisingly little has been added to the knowledge of idiopathic pericarditis in the many subsequent ones beyond those items, in this case relatively unimportant, which have been added from the use of various laboratory procedures as year by year they have been developed. At the end of these decades its exact etiology remains undemonstrated.

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Original Communications

DISTURBANCES IN CARDIAC MECHANISM OF SEVERAL HOURS' DURATION COMPLICATING CARDIAC VENOUS CATHETERIZATION

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THE frequency with which cardiac arrhythmias may occur as a complication of venous catheterization of the heart was indicated by Goldman, Blount, Friedlich, and Bing.[1] These workers observed the electrocardiograms of their subjects continuously during catheterization of the heart. All their subjects except one developed some transient cardiac arrhythmia. In most of them, the arrhythmia terminated promptly following withdrawal of the catheter. In one patient who developed right bundle branch block, the disturbance in mechanism persisted following termination of the procedure. One other subject developed fatal ventricular fibrillation.

The purpose of this paper is to indicate the frequency and duration of disturbances in cardiac mechanism which we have observed during cardiac catheterization and which persisted following withdrawal of the catheter. The material consists of 110 consecutive cardiac catheterizations performed upon 106 patients from the medical wards of the Cincinnati General Hospital. Venous catheterization of the right side of the heart was performed in the manner of Cournand and Ranges.[2] In all but the first few subjects the three standard electrocardiographic leads and the three unipolar extremity leads were recorded prior to insertion of the catheter into the antecubital vein. Intermittent recordings of the electrocardiogram were made during catheterization in all subjects. During manipulation of the catheter, the electrocardiogram of the subject was observed carefully, a direct-writing type of electrocardiograph being used. In ninety-seven of the procedures, the catheter was advanced into the pulmonary artery. In nine instances the catheter was advanced no farther than the right ventricle. In four instances it was impossible to advance the cardiac catheter farther than the right atrium. Location of the catheter tip was observed by fluoroscopy and confirmed by a pressure tracing taken with the Hathaway blood

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pressure recording apparatus. A twelve-lead electrocardiogram was made following the procedure if any disturbance in cardiac mechanism was present after the catheter was removed.

RESULTS

When the catheter tip entered the right atrium, auricular or nodal premature contractions were seen almost invariably. When the tip entered the right ventricle, ventricular premature contractions developed in almost every instance. No arrhythmias arose which necessitated withdrawal of the catheter for their reversion.

The following patients developed disturbances in cardiac mechanism which were still present following withdrawal of the catheter.

CASE 1.—A. B. was a 37-year-old man convalescing from right lower lobe pneumonia. The heart was normal to physical examination, roentgenogram, and electrocardiogram. Cardiac catheterization was performed April 28, 1950, the catheter entering the pulmonary artery. Complete right bundle branch block developed which was noted following withdrawal of the catheter and which was still present four hours later. After the lapse of twelve hours the electrocardiogram had returned to its former normal appearance.

Case 2.—R. E. was a 59-year-old man suffering from hypertensive cardiovascular disease and congestive heart failure. Cardiac catheterization was done on May 23, 1950. The catheter tip was advanced into the pulmonary artery. Complete right bundle branch block developed and endured following removal of the catheter. Twelve hours later, the bundle branch block had vanished.

CASE 3.—C. P. was a 30-year-old man convalescing from bronchopneumonia. The heart was normal to physical examination, roentgenogram, and electrocardiogram. On June 13, 1950, venous catheterization of the pulmonary artery was accomplished. During passage of the catheter tip through the right atrium, auricular fibrillation with a rather slow ventricular rate of 75 developed. This arrhythmia had disappeared three hours after termination of the study.

CASE 4.—C. H. was a 33-year-old man suffering from pleural effusion, presumably tuberculous. The heart was normal to physical examination, electrocardiogram, and roentgenogram. Cardiac catheterization was performed on April 21, 1950, the catheter tip entering the pulmonary artery. Complete right bundle branch block developed during the procedure and was present following withdrawal of the catheter. Fig. 1 shows in the upper row the normal six-lead electrocardiogram of this subject immediately prior to catheterization. The middle row indicates the development of complete right bundle branch block and was taken just after catheterization. Note the appearance of a wide S_1, the wide late R wave in aV_R, the large R wave in V_1 with delayed intrinsicoid deflection of 0.11 second, and the wide S wave in V_6. The lower line of electrocardiographic complexes indicates the return to normal in this subject four hours later.

CASE 5.—F. B. was an 18-year-old girl suffering from sickle-cell anemia. Although the electrocardiogram was normal, the heart showed some generalized enlargement roentgenographically. Cardiac catheterization was performed Jan. 17, 1951. The tip of the catheter entered the pulmonary artery. Right bundle branch block developed during the procedure. Fig. 2 indicates in the second row the electrocardiogram taken just after withdrawal of the cardiac catheter, showing the development of right bundle branch block. Note the appearance of a wide S_1, wide R′ in aV_R, and the classical RsR′ pattern in V_1. The intrinsicoid deflection in V_1 was delayed to 0.08 second. The arrhythmia had disappeared by the following morning. Unfortunately, the electrocardiogram of that morning is not available. The lower line of Fig. 2 indicates the return to normal rhythm. This record was taken March 22, 1951.

CASE 6.—A. B., a 46-year-old man, was suffering from central nervous system syphilis, optic atrophy, and compensated hypertensive cardiovascular disease. Cardiac catheterization was done

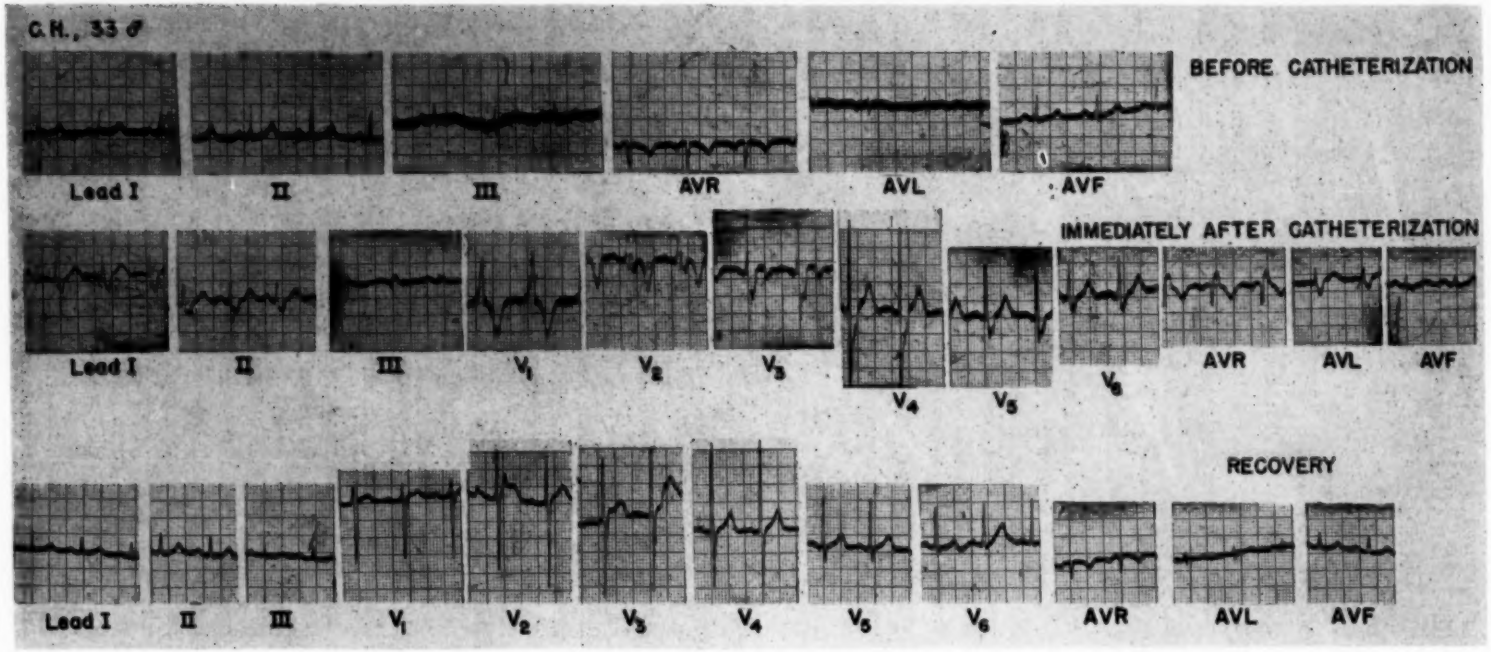

Fig. 1.—The electrocardiograms of subject C. H., showing normal electrocardiogram before catheterization, the presence of right bundle branch block immediately following catheterization, and the disappearance of right bundle branch block four hours after catheterization.

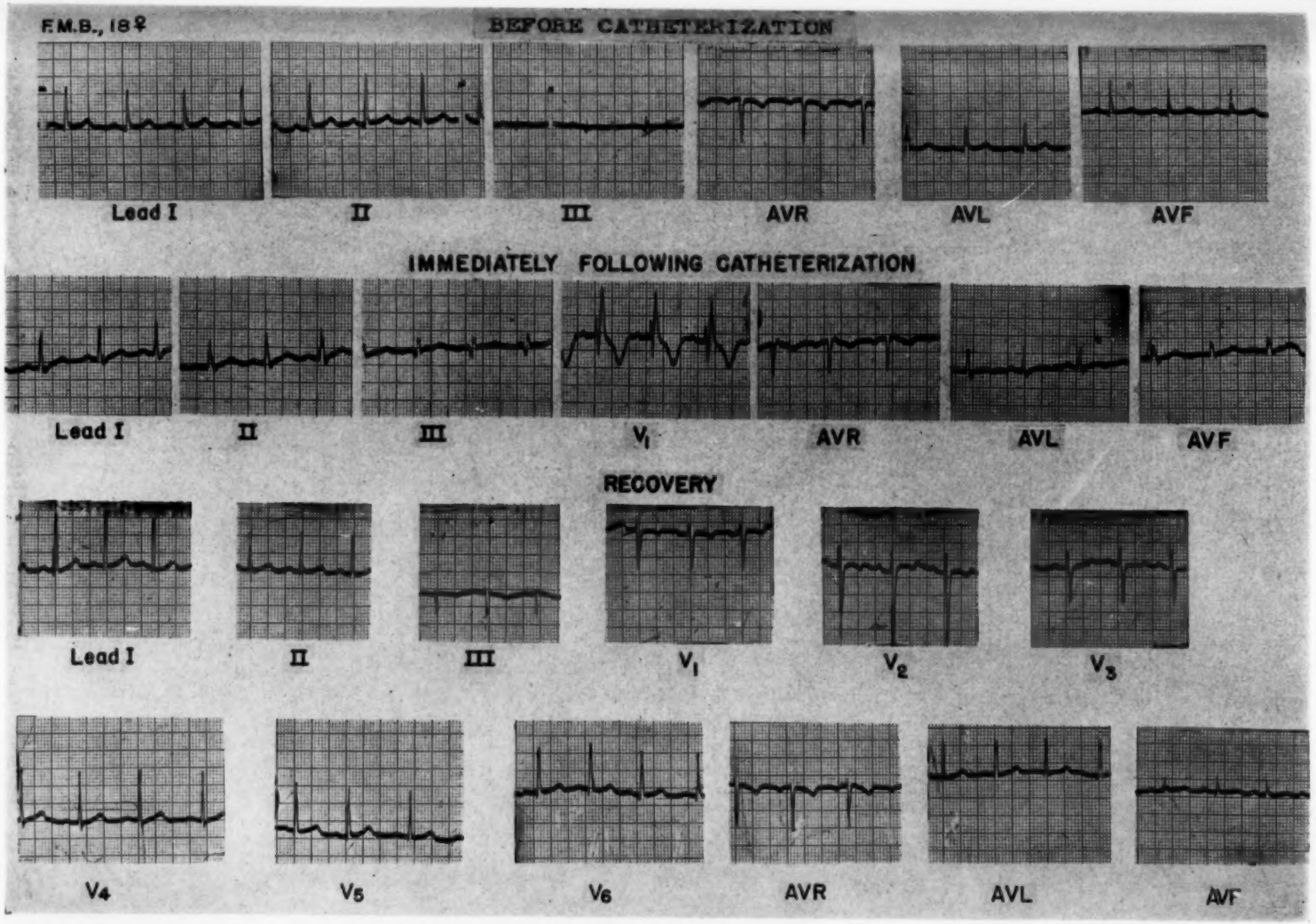

Fig. 2.—The electrocardiograms of subject F. B., showing the normal electrocardiogram before catheterization, the presence of right bundle branch block immediately following catheterization, and the disappearance of the right bundle branch block.

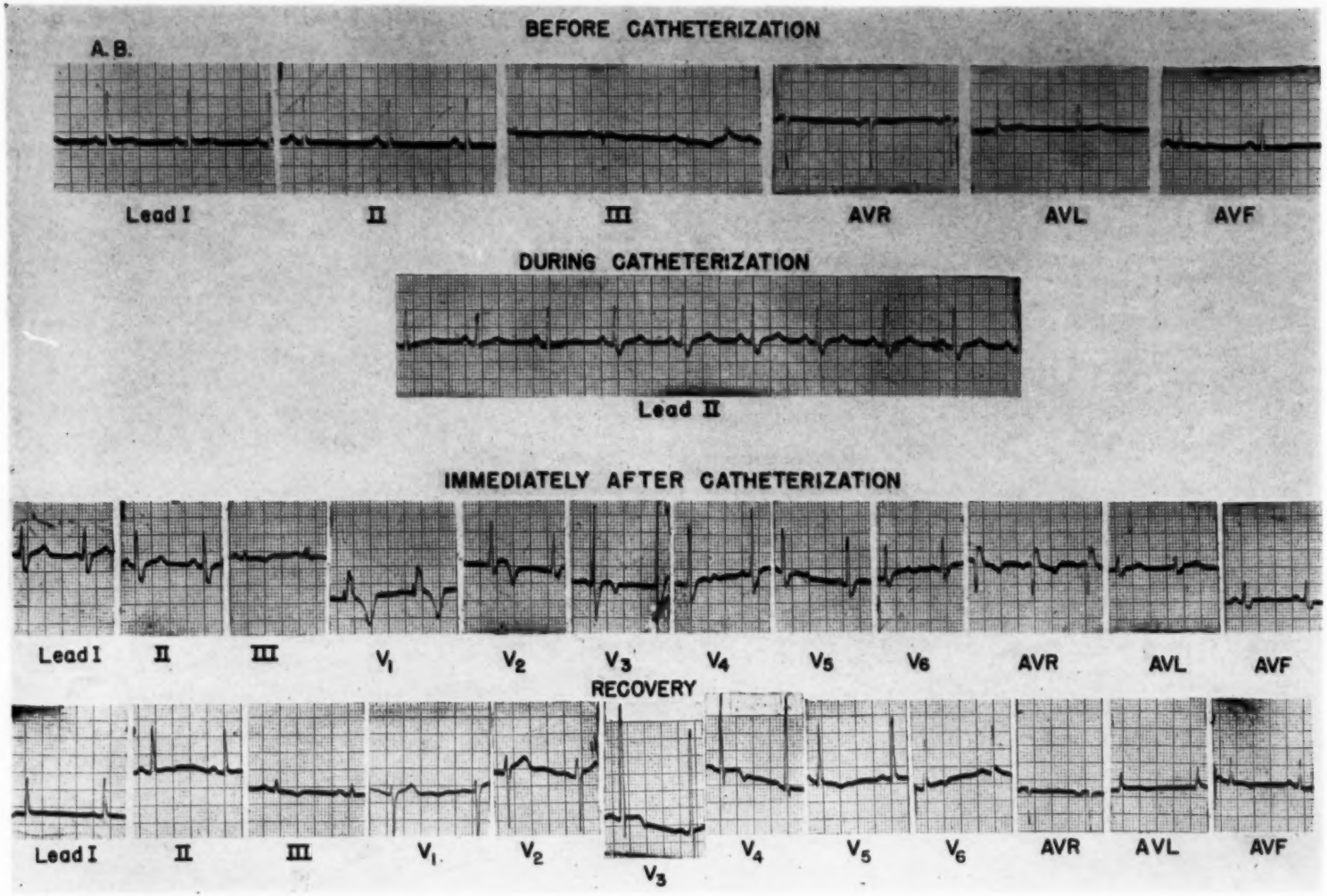

Fig. 3.—The electrocardiograms of subject A. B., showing the electrocardiogram with flattening of T_1 and inversion of T_2 before catheterization. The development of right bundle branch block is shown during catheterization in Lead II. The twelve-lead electrocardiogram immediately after catheterization demonstrates the right bundle branch block. In the fourth line is shown the return to normal mechanism ten hours after cardiac catheterization.

on Feb. 23, 1951. The catheter tip entered the pulmonary artery. Complete right bundle branch block developed and persisted following withdrawal of the catheter. Fig. 3 in the upper line shows the precatheterization electrocardiogram. The second line indicates the moment of development of right bundle branch block during catheterization of the right ventricle (Lead II). The third line shows the persistence of right bundle branch block following withdrawal of the catheter. The bottom line shows the disappearance of right bundle branch block ten hours after removal of the cardiac catheter.

CASE 7.—G. A. was a 60-year-old man suffering from emphysema, cor pulmonale, and congestive heart failure. Cardiac catheterization was done Feb. 27, 1951. The catheter tip entered the pulmonary artery. As the catheter was withdrawn through the right ventricle, frequent and persistent ventricular premature contractions with long runs of bigeminal rhythm developed. This arrhythmia persisted following removal of the catheter. One hour later, the arrhythmia had disappeared.

CASE 8.—F. T. was a 52-year-old man suffering from carcinoma of the lung. The electrocardiogram showed nonspecific abnormalities before catheterization. Venous catheterization of the right side of the heart and pulmonary artery was carried out March 30, 1951. During the procedure right bundle branch block developed and persisted following withdrawal of the cardiac catheter. Two hours and thirty minutes later, the bundle branch block had disappeared completely.

One other subject, a 46-year-old man suffering from pulmonary tuberculosis, developed right bundle branch block when venous catheterization was done. The catheter tip in this instance entered the pulmonary artery. Right bundle branch block developed as the catheter was withdrawn through the right ventricle and persisted after the catheter tip was withdrawn into the right atrium. Unfortunately, this subject was a patient from another hospital, and follow-up electrocardiograms are not available to indicate the duration of the bundle branch block.

Fig. 3.—The electrocardiograms of subject A. B., showing the electrocardiogram with flattening of T_1 and inversion of T_2 before catheterization. The development of right bundle branch block is shown during catheterization in Lead II. The twelve-lead electrocardiogram immediately after catheterization demonstrates the right bundle branch block. In the fourth line is shown the return to normal mechanism ten hours after cardiac catheterization.

DISCUSSION

As indicated in the introduction, the occurrence of some disturbance in cardiac mechanism during the introduction of a venous catheter into the heart is almost universal. The arrhythmia ordinarily ceases abruptly when the exploring catheter is withdrawn. The persistence of disturbed rhythm after withdrawal of the catheter from the heart is therefore not common. Dexter and associates[3] observed auricular fibrillation lasting thirty minutes after withdrawal of the catheter in two instances. Burchell and Wood[4] also reported one case of auricular fibrillation and one case of auricular tachycardia persisting after catheterization. Chapman[5] observed two cases of induced auricular tachycardia persisting two and four hours, respectively, following termination of cardiac catheterization. Johnson and co-workers[6] reported a case of auricular tachycardia lasting two hours after catheterization. Zimdahl[7] reported a case of nodal tachycardia persisting thirty minutes after withdrawal of the catheter from the heart. Simonson[8] reported in detail a case of right bundle branch block induced by cardiac catheterization. The bundle branch block persisted for one hour after termination of the procedure. Michel and co-workers[9] reported two instances of arrhythmia persisting following cardiac catheterization in 133 consecutive cases. In one case an intraventricular block occurred and persisted for several hours. The other case was an ill-defined arrhythmia in an infant, leading to death in two hours. Cournand and co-workers[10] reported one case of auricular tachycardia persisting for a short while after withdrawal of the catheter. Wood[11] reported

two cases of ventricular fibrillation, one fatal, as a result of cardiac catheterization. Southworth and co-workers[12] reported a case of ventricular fibrillation complicating heart catheterization which persisted forty-five minutes and was reverted to sinus rhythm by procaine and electric shock. Bruce and co-workers[13] reported a case of ventricular tachycardia as a complication of cardiac catheterization in a case of Wolff-Parkinson-White syndrome. The ventricular tachycardia persisted nine hours in their patient, after which conversion to supraventricular tachycardia was accomplished. This arrhythmia then persisted six more hours until sinus rhythm was obtained.

Seven of our nine patients had right bundle branch block persisting following catheterization. Kert and Hoobler[14] have postulated that this is due to pressure of the catheter upon the subendocardial right bundle branch or upon the subendocardial Purkinje plexus. In those cases where a disturbance in mechanism lasts for several hours following withdrawal of the catheter perhaps pressure has interfered with the physiological function of the cells temporarily, but has not produced permanent necrosis. The possibility of a small subendocardial hemorrhage must also be considered. Dexter and associates[3] noted no damage to the endothelium, valve leaflets, papillary muscles, or chordae tendineae of dogs purposely exposed to traumatic catheterization of the right side of the heart. Ellis, Essex, and Edwards,[15] however, found thrombotic lesions in the right atrium or right ventricle in nine of sixteen dogs subjected to venous catheterization in the manner usually employed in human beings. The failure of Dexter to find similar lesions in ten autopsied patients who died soon after cardiac catheterization, but from other causes, suggests that thrombotic lesions do not occur in the human subject with the same frequency as in the dog. Michel felt that the arrhythmia was not necessarily provoked by the catheter tip, but might be produced by lateral pressure from a more proximal portion of the instrument; Michel felt further that the incidence of cardiac arrhythmias following venous catheterization of the heart was significantly greater in those subjects who had electrocardiographic abnormalities prior to the procedure.

We, too, have observed that premature contractions, especially right ventricular, are much more common when the diseased heart is irritated by the catheter tip than when the subject with a normal heart is studied. In the present group of disturbances in mechanism persisting following catheterization, five of the nine patients had normal electrocardiograms, although one of the five (F. B.) with sickle-cell anemia had cardiac enlargement on fluoroscopy. In the entire group of 110 procedures 40 were done upon normal hearts and 70 upon diseased hearts. We were thus unable to confirm the impression that persistent arrhythmia is more likely to develop after cardiac catheterization in the diseased than in the normal heart.

In the eight of our nine patients who were carefully followed, the disturbance in cardiac mechanism invoked by cardiac catheterization had disappeared within twelve hours after the procedure. The cardiac arrhythmias induced by catheterization which are enumerated in the literature, except for the case of Bruce and co-workers,[13] disappeared in less than twelve hours where the duration is given.

However, three cases of fatal arrhythmia are described. It would seem likely that if the arrhythmia induced by catheterization of the heart does not produce profound disturbance of cardiac function, the prognosis is good, and the arrhythmia may usually be expected to disappear in twelve hours or less.

It should be emphasized again that catheterization of the human heart is not a procedure to be undertaken lightly. In our series, 8 per cent of such catheterizations were complicated by cardiac arrhythmias persisting after the study. Although spontaneous recovery took place in our cases, three fatal arrhythmias were found in the literature and more have undoubtedly occurred. Constant fluoroscopic and direct-writing electrocardiographic observations are believed essential to the procedure and are the least that should be done for the safety of the patient.

One should be prepared to treat ventricular fibrillation if it arises. Southworth and associates[12] suggested that ventricular fibrillation be handled as follows: Five cubic centimeters of 1 per cent procaine may be injected through the catheter, and the catheter is then withdrawn. If reversion does not occur, the following procedure should be adopted: Respiration should be carried out by manual compression of the chest, or better, by use of an endotracheal tube and a respirator. Circulation may be maintained by manual compression of the heart, the hand being inserted through an anterolateral thoracic incision. Twenty cubic centimeters of 1 per cent procaine are injected directly into the heart. Then repeated electric shocks of 135 volts, lasting ½ to 1½ second are applied to the heart. The exact amperage used is unknown, but is near 5 amperes.

SUMMARY

1. As a complication of 110 venous catheterizations of the right side of the heart in 106 human subjects, the following disturbances in cardiac mechanism were found following withdrawal of the catheter: right bundle branch block in seven cases, auricular fibrillation in one case, and frequent ventricular premature contractions in one case.

2. In each of eight cases where follow-up electrocardiograms were made, the arrhythmia disappeared within twelve hours.

3. In these instances, arrhythmia developed as often in normal as in diseased hearts.

4. A study of our cases and those reported in the literature indicates that if the induced arrhythmias following catheterization of the heart are not fatal, they may usually be expected to disappear within twelve hours.

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MYOCARDIAL DAMAGE FOLLOWING INADVERTENT DEEP CANNULATION OF THE CORONARY SINUS DURING RIGHT HEART CATHETERIZATION

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ALTHOUGH cardiac catheterization has become an established clinical procedure, the complications which may occur are still being defined. Disorders of cardiac rhythm constitute the most important group of complications of right heart catheterization, owing to their frequency[1,2] and to the fact that a dysrhythmia thus induced may be persistent[3] and of a serious type. Observations on dogs[4] have shown that myocardial damage may be produced by manipulation of a catheter within the heart, but in man such lesions have been infrequent[2] and usually limited to contusions of the endocardium and mural thrombosis.

Another complication, hitherto not stressed, is myocardial damage following deep catheterization of the coronary venous tree. There follows the report of a patient who became seriously ill following deep catheterization of the coronary veins. Reference will be made to several similar cases which have occurred in another laboratory.

The patient, a 61-year-old white man without clinical evidence of cardiovascular disease, was hospitalized because of anorexia and weight loss. Extensive clinical and roentgenographic examination supported the clinical impression of mild pulmonary emphysema and disclosed no evidence of other disease.

Cardiac catheterization was done on Sept. 15, 1950, without difficulty. The catheter was passed easily into the right pulmonary artery. By standard techniques, intracardiac and femoral arterial pressures were recorded, and cardiac output was determined at rest and during the last of four minutes of exercise (flexion of one lower extremity every three seconds). The results of these determinations are tabulated, and the electrocardiogram is shown at *A* in Fig. 1.

The patient then received injections of 10 mg. of desoxycorticosterone acetate intramuscularly daily, with supplementary sodium chloride by mouth. After twenty-five days, the patient had gained 11 pounds and developed minimal ankle edema.

On October 11 repeat hemodynamic studies were performed. The control electrocardiogram is shown in Fig. 1, *B*. A 9½ F double-lumen catheter was employed. As the catheter was advanced from the right atrium, it appeared to enter the right ventricle and approach the pulmonary conus. When it seemed that the tip had reached a point about 7 inches beyond the tricuspid valve,

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TABLE I. HEMODYNAMIC FUNCTIONS, AT REST AND DURING THE LAST MINUTE OF FOUR MINUTES OF EXERCISE

	RESPIRATORY RATE (PER MINUTE)	VOLUME VENTILATED (L. PER MINUTE, BTPS)	OXYGEN CONSUMPTION (C.C. PER MINUTE, STP)	ARTERIAL OXYGEN CONTENT (VOLUME %)	MIXED VENOUS OXYGEN CONTENT (VOLUME %)	ARTERIO-VENOUS OXYGEN DIFFERENCE (VOLUME %)	CARDIAC OUTPUT (L. PER MINUTE)	PRESSURES (MM. Hg)		
								RIGHT ATRIUM	PULMONARY ARTERY	FEMORAL ARTERY
9/15/50 Rest*	32	13.7	178	19.2	13.4	5.8	3.1	0	20/5	99/52
Exercise	30	11.5	324	19.1	12.1	7.0	4.6		29/15	121/63
10/11/50 Rest*	32	11.3	208	16.0	9.9	6.1	3.3	6		128/69
Exercise	22	14.2	315	16.0	7.9	8.1	3.9	7		130/73

*Average of three determinations. Surface area 1.48 M.²

the pressure wave from the catheter tip was recorded simultaneously with Lead II of the electrocardiogram and found to be characteristic of the coronary sinus. The catheter was obviously deep in the coronary venous tree, probably in the great cardiac vein; it was withdrawn immediately into the right atrium. The three standard leads of the electrocardiogram were then recorded and disclosed fusion of the ST segment with the T wave and depression of J in Leads I and II (*C*). Lead II of this tracing was identical with that recorded when the catheter was in the cardiac vein.

At the time that the catheter tip was deep in the cardiac vein, the patient complained of pain in the back; this disappeared when the catheter was withdrawn to the right atrium. The catheter had been in the coronary venous tree for a total of five minutes.

After several additional unsuccessful attempts to catheterize the right ventricle, the tip of the catheter was fixed in the mid-right atrium, the femoral artery was cannulated, and the hemodynamic determinations were carried out. The patient tolerated the procedures, including leg exercise, fairly well although he was somewhat restless and had repeated paroxysms of dry cough. The determinations were completed about two hours after the coronary sinus had been entered; the data are tabulated.

Removal of the catheter at the end of the observation period was accompanied by marked pain in the arm and shoulder along the course of the vein. The needle was removed from the femoral artery several minutes later and the cannulation site firmly compressed for five minutes; during this time the antecubital vein was ligated and the incision sutured. It was then noted that the patient had become quite restless, and he began to yawn. The extremities were cold, and the brachial artery pressure was found to be 80/60 mm. Hg. The pillows were removed from under the patient's head, and oxygen was administered. Within fifteen minutes the blood pressure had returned to 100/70 mm. Hg, and the skin became warmer. An electrocardiogram (*D*) at this time disclosed an isoelectric T_1 and lower voltage of the QRS than in the control. About eighty minutes after the syncopal episode the patient complained of pressing pain in the upper retrosternal area. The blood pressure was then 90 mm. Hg systolic; the diastolic was indeterminate. Thirty minutes later an electrocardiogram (*E*), including extremity and precordial leads, revealed in addition to the abnormalities already described an inverted T_{AVL}. Precordial pain became severe and apprehension marked. Morphine sulfate (10 mg.) calmed the patient, but the blood pressure remained low and the skin was pale, cold, and clammy. The patient was placed in an oxygen tent. Four hours after the initial episode of hypotension, the pulse and blood pressure were unobtainable and the heart inaudible. During the next eight hours, in the course of which he received a liter of blood intravenously as treatment for shock, the patient gradually improved, and thirteen hours after the onset of syncope he was alert; the blood pressure was 105/70 mm. Hg, the ventricular rate 80 per minute.

The next morning, October 12, the patient appeared generally to be in fair condition but again complained of precordial and substernal sticking pain. The blood pressure was 140/80 mm. Hg. Later in the day, the temperature rose to 102.6° F. and the ventricular rate to 110 per minute. Pulsus paradoxus appeared, and there were many medium moist râles in both lung bases. The neck veins were full and exhibited retrograde filling suggesting congestive heart failure. The patient was considered to have bronchopneumonia, and penicillin administration was begun. The white blood count was normal and remained so during the following days. An electrocardiogram (*F*) disclosed further changes: diphasic T waves in the standard leads and a low T_{AVL}.

On the second day after catheterization the patient was still febrile. He had a persistent hacking and scantily productive cough, but the chest pain had disappeared. The electrocardiogram (*G*) revealed slightly more positive T waves and elevation of J_1 and J_2. On the following day, October 14, a pericardial friction rub was heard, and the electrocardiogram (*H*) disclosed further elevation of J_1 and J_2.

Despite the addition of aureomycin to therapy, fever between 101 and 102° F. persisted through October 17, six days following the catheterization, then generally remained below 100° F. The lung fields very slowly cleared of râles, and the cough finally ceased. The electrocardiogram (*I*) on October 17 disclosed T waves which were almost identical with those of the control tracing and return of the J waves toward the isoelectric line.

On October 25 the patient developed a sudden, constricting retrosternal chest pain which lasted one-half hour and required Demerol for control. There was, however, no objective change

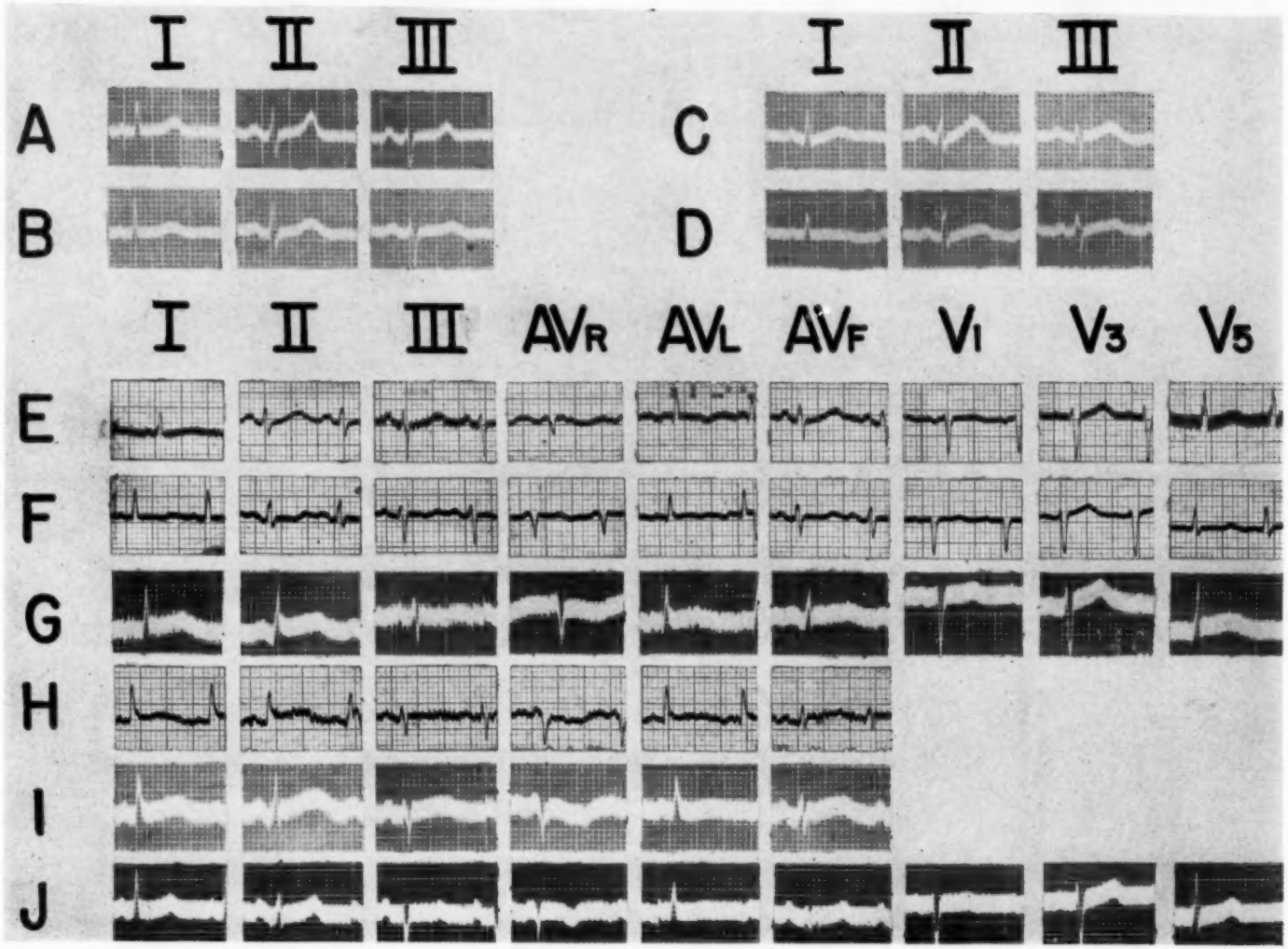

Fig. 1.—Representative portions of pertinent electrocardiograms taken from the patient whose course is described. The letters identify the tracings referred to in the text.

on physical examination, no fever, and subsequent electrocardiograms revealed no change. Thereafter, the patient did well clinically and was eventually discharged. The final electrocardiogram, recorded on December 7, revealed almost complete restoration to normal (*J*).

DISCUSSION

McMichael and Mounsey[5] reported five instances of adverse reaction to deep catheterization of the coronary venous tree. In one case the catheter apparently perforated a coronary vein and entered the pericardium. All patients immediately developed pain in the precordium or back. This pain was singularly persistent, in one patient recurring for a week although the status was otherwise apparently improving. Three patients promptly developed peripheral vascular collapse, and these three subsequently developed the electrocardiographic changes usually associated with pericarditis. (These three patients did not include the one in whom the catheter entered the pericardial space.) All patients survived.

The patients of McMichael and Mounsey and the one here described probably all belong to the same group, although our case differed in that there was an interval of several hours between catheterization of the coronary venous tree and onset of syncope. For this reason there was at first some uncertainty about the etiological relationship between the two events, particularly as the painful manipulation of the vessels at the end of the determinations might have evoked syncope through a vasovagal reflex. Corday and associates[6] have shown that hypotension may precipitate acute ischemia in parts of the myocardium supplied by narrowed arteries. An infarct might thereby evolve, with production of the electrocardiographic changes described. With the report of the cases of McMichael and Mounsey, however, it would seem that the collapse was indeed due to cannulation of the coronary venous tree. The fact that electrocardiographic changes developed during the cannulation adds weight to this interpretation.

The pathological lesion in this syndrome is not clear. Goodale and coworkers[4,7] demonstrated that, following deep catheterization of the coronary venous tree in dogs, there are frequently found large hemorrhages in the myocardium and occasionally thrombosis of the injured veins, with electrocardiographic evidence of pericarditis. Small areas of myocardial fibrosis were found in dogs autopsied weeks after the procedure. Similar lesions may be supposed to have occurred in these patients, but it is curious that the reactions should have been so prompt and so severe.

SUMMARY AND CONCLUSIONS

A case is reported in which clinical evidence of myocardial damage developed following cardiac catheterization, in the process of which the catheter had inadvertently been advanced deeply into the coronary venous tree for several minutes. Electrocardiographic changes developed immediately on introduction of the catheter and subsequently assumed the configuration characteristic of pericarditis. That this is not an isolated, rare event is illustrated by reference to several cases which occurred in another laboratory.

It is probable that catheterization of the coronary venous system is dangerous only if the catheter has a relatively large outside diameter and is inserted deeply.

Several investigators[4,7] have shown that inserting the catheter tip only a short distance into the coronary sinus may be done safely, and there is evidence[8] that the coronary venous tree may tolerate a small catheter even if inserted deeply.

It is therefore suggested that great care be taken in catheterizing the right ventricle and that the course of the catheter be checked by fluoroscopy in the right oblique position and by observing the pattern of the pressure tracing from the catheter tip immediately after it has appeared to traverse the tricuspid valve.

The authors wish to thank Dr. J. McMichael and Dr. J. P. D. Mounsey for their generosity in making available case reports from their laboratory.

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OBSTRUCTING LEFT AURICULAR THROMBI

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ANTE-MORTEM formation of thrombi within the auricles of the heart is not uncommon, particularly in individuals dying of rheumatic heart disease.[1-3] Usually, these thrombi are important only as sources of peripheral emboli. On occasion, however, auricular thrombi may obstruct the general circulation.

In 1814, William Wood[4] detected at necropsy a large ball-valve thrombus (1½ inches in diameter) in the left auricle which had obstructed the flow of blood, he believed, through a stenotic mitral orifice. Von Ziemssen[6] and others have felt that a clear distinction between large free and pedunculated auricular thrombi should not be made since both could produce the same symptoms.

In our necropsy records, we studied the post-mortem findings and later the clinical histories of four patients. Two had died with a large pedunculated left auricular thrombus and two with a free thrombus in the left auricle.

CASE REPORTS

CASE 1.—A. K., a 67-year-old white woman, was admitted to the hospital with advanced, chronic rheumatoid arthritis. The course in the hospital was uneventful for four years except for a persistent pyelonephritis. On March 5, 1944, she became acutely ill with a temperature of 103° F. Cyanosis of the lips was present. Medium moist râles and rhonchi were heard at both lung bases. She was thought to have bronchopneumonia, but in spite of sulfadiazine therapy her condition deteriorated and she died nine days after the onset of the acute illness. Slight cyanosis was occasionally present during the terminal period. An apical systolic murmur was heard prior to death, but a diastolic murmur was never noted. Regular sinus rhythm was always present. Death was not sudden.

At post-mortem examination the heart weighed 310 grams. The right ventricular wall was 3 mm. thick. The left auricle was markedly dilated. The mitral valve measured 8 cm. with fused and thickened leaflets with short thick chordae tendineae. On the auricular surface of the anterior leaflet there was a small ulcerated area with a small vegetation. Lying free in the auricular cavity was a large, round thrombus. The left ventricle was dilated slightly, and there were a few small mural thrombi adherent to the endocardium of the lower one-half of the ventricle. The aortic valve showed minimal sclerosis. A large thrombus extended to, but did not occlude, the common iliac arteries. Chronic, bilateral pyelonephritis was also found. Evidence of embolic phenomena was not found.

Microscopically, a Gram stain of the mitral valve and the mitral thrombi of the left ventricle showed clumps of gram-positive bacteria. Cultures grew *Streptococcus viridans* and *Staphylococcus*

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aureus, the latter probably a contaminant. The ball thrombus was unfortunately not stained for bacteria.

CASE 2.—G. P., a 52-year-old white man with rheumatic heart disease, was admitted to the hospital in congestive heart failure. Auricular fibrillation and a systolic and diastolic mitral murmur were noted on admission.

Under treatment, the sacral edema disappeared but dyspnea increased. Pleural fluid was removed from the right side of the chest on several occasions. He frequently complained of substernal pain, and there was one episode of severe right upper quadrant pain. One resident noted that "he was more comfortable lying on his back than in a position of orthopnea." The patient died suddenly five weeks after admission.

At post-mortem examination, the heart weighed 460 grams. The right auricle and ventricle were dilated. The right ventricular wall was 6 mm. thick. The left auricle was dilated with irregular raised areas present on the posterior wall. A large circular thrombus 3.5 cm. in diameter was lying free in the left atrium, apparently detached from an ulcerated area at the free margin of the anterior leaflet of the mitral valve. The mitral orifice was extremely stenotic with thickened fused leaflets. The left ventricle was dilated, but not hypertrophied. The aortic cusps were normal. Small infarcts were present in the lungs, kidneys, and brain.

Microscopically, the left auricular endocardium was irregular and thickened by fibrous tissue with a diffuse round-cell infiltration of the deeper layers.

CASE 3.—W. E., a 59-year-old white woman, was admitted to the hospital because of progressive weakness and epigastric fullness. No history of cardiac disease was obtained.

On physical examination, the blood pressure was 105/70 mm. Hg. There was no cyanosis or dyspnea. The heart was not enlarged. An apical systolic and diastolic murmur was heard. Auricular fibrillation was present. Four months after admission, she had a cerebrovascular accident with a resultant left hemiplegia. She survived this episode, but one month later developed pneumonia and died. All blood cultures taken were negative.

Post-mortem examination revealed 300 c.c. of serosanguineous fluid in the left pleural cavity. There were large wedge-shaped hemorrhagic infarcts in the middle and upper lobes of the right lung with small infarctions in the left lower lobe. In the considerably dilated left auricle there was a spherical thrombus, 4.5 cm. in diameter, slightly adherent to the endocardium, which had a tonguelike continuation extending over the auricular surface of the posterior leaflet of the mitral valve and another projection into the narrow mitral orifice. The mitral valve was thickened, distorted, and stenosed. The aortic cusps showed some fusion at the commissures with thickening. The auricular endocardium seemed thickened in the vicinity of the attached thrombus. The right ventricle was 3 mm. thick, while the left ventricle measured 14 mm. Moderate coronary sclerosis was present. The spleen and kidneys had many small infarcts. There was right cerebral encephalomalacia secondary to a cerebral embolus. Bacterial stains of the mitral and aortic valves were negative.

CASE 4.—G. S. was a 64-year-old woman with hypertension and a history of diabetes mellitus for twenty years. For three months before admission she was treated at another hospital for peripheral vascular disease of the right foot and for progressive dyspnea associated with a recurrent right hydrothorax.

In spite of therapy, the patient remained in congestive heart failure, and there were progressive gangrenous changes in the right toes. Although facial cyanosis was noted several times during the illness, at no time was it conspicuous. She died four months after admission. Regular sinus rhythm was present throughout the course.

At post-mortem examination the right pleural cavity contained 3,000 c.c. and the left 1,000 c.c. of clear amber fluid. Marked pulmonary congestion was present bilaterally. The heart weighed 720 grams. All the heart cavities were moderately dilated. The right auricle contained a few small thrombi in the appendage. The left auricle contained a spherical thrombus 6 cm. in diameter which occupied most of the auricular cavity. It was attached to the auricular wall anteriorly by a pedicle measuring 1.5 cm. in diameter and 0.5 cm. in length. The mitral valve measured 9.5 cm. in circumference, and its leaflets were thickened with slight rolling of the free

edges. There were numerous atheromatous plaques with marked narrowing in both the left and right coronary arteries and branches. About 1,000 c.c. of ascitic fluid were present. Microscopically, the mitral valve showed vascularization and lymphocytic infiltrations. The auricular wall beneath the pedicle of the thrombus showed numerous small thin-walled vessels with a small number of surrounding lymphocytes and plasma cells in a greatly thickened endocardium.

DISCUSSION

Von Ziemssen,[6] in 1890, was the first to attempt to attribute a group of clinical signs to the diagnosis of ball-valve thrombus. He made no effort to differentiate a ball thrombus from a pedunculated thrombus and felt that these could not be distinguished in vivo. He suggested that circumscribed gangrene of the feet and cadaveric coldness accompanied by an obliteration of the arterial pulses in the lower extremities in a patient with mitral stenosis might be attributed to the greatly diminished flow of blood from the left ventricle resulting from an obstruction, by a thrombus, of the stenotic mitral valve. Elson[7] has considered transitory alterations in the peripheral circulation, such as marked cyanosis, extreme coldness, or gangrene of the fingers and toes of several extremities, particularly suggestive of an obstructive auricular thrombus. With dislodgment of the thrombus, the signs could disappear only to recur when the mitral orifice was again occluded. Ernstene and Lawrence[8] described a patient with an occluding left auricular thrombus who during attacks of paroxysmal dyspnea preferred to lie flat in bed because sitting up caused prompt loss of consciousness.

Changing mitral murmurs have rarely been observed with a ball or pedunculated thrombus[9-11] but when present, the change may be dramatic. Although giddiness and syncope are not unusual cardiologic symptoms, they would appear to be more common with occluding left auricular thrombi.[7,10,12,13] Reports of sudden death ascribed to ball thrombi of the auricle also have appeared, being present in ten of twenty-one cases reviewed by Abramson.[14]

With few exceptions,[19] the great majority of patients with obstructing left auricular thrombi have had rheumatic heart disease and mitral stenosis. In considering the clinical picture of obstructing left auricular thrombi, von Recklinghausen[15] declared that no signs "have been elicited in a case of mitral stenosis with a ball or loose thrombus that might not have occurred in a case of simple mitral stenosis of high grade." It is interesting to note, though, that in patients who have had no evidence of heart disease and who develop polypoid tumors of the left auricle (which may obstruct the mitral opening), a clinical picture may be produced[16,17] which is strikingly similar to that ascribed to an obstructing left auricular thrombus.

The occurrence of systemic embolic phenomena is common in cases of obstructing auricular thrombi. Unfortunately, this is of little diagnostic value since the great majority of the cases reported in the literature present mitral stenosis and auricular fibrillation,[11] in both of which there is a high incidence of emboli.

Although all four of our patients had large thrombi which seemed capable of producing mitral obstruction and the syndrome often ascribed to ball or pedunculated auricular thrombi, only our second patient, who preferred to lie flat in bed when dyspneic and who died suddenly, showed any signs which we could

ascribe directly to the thrombus occluding the mitral orifice. However, from these and previously reported cases one should not conclude that obstructing thrombi do not produce a distinct clinical picture; rather, they may exist without producing a definite syndrome. It is also true that a tight mitral stenosis may present all of the signs and symptoms of an occluding auricular thrombus.[14,17] Nevertheless, as Abramson has pointed out, the mere fact that a suggestive syndrome has often occurred with an obstructing thrombus justifies the suspicion which should exist in the examiner's mind when he is confronted with this oft-repeated clinical picture. Accurate ante-mortem diagnosis has now assumed some importance since the great advances made in cardiac surgery suggest the possibility of surgical intervention. At present, the clinical diagnosis of an obstructing auricular thrombus is extremely difficult to make and more difficult to prove. However, with greater attention to the condition, better diagnostic methods, it is hoped, may be found.

CONCLUSIONS

1. Four patients are presented who were found to have large free or pedunculated auricular thrombi capable of occluding the mitral orifice.
2. The literature on ball and pedunculated auricular thrombi is briefly reviewed.
3. In only one of the four patients presented did it seem that the large thrombus played a definite role in the patient's clinical course or findings.
4. Since surgical intervention is potentially of value, means for more accurate diagnosis of obstructing auricular thrombi should be sought.

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SERUM ELECTROLYTES AND THE ELECTROCARDIOGRAM

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THE effect of variations in the concentration of serum electrolytes, particularly calcium and potassium, on the form and duration of the repolarization wave of the electrocardiogram is a subject of current interest. Changes associated with low serum potassium levels, such as diminished amplitude of the T wave, prolongation of the Q-T interval, depression of the ST segment, and the presence of large U waves, have been described.[1-6] The high, peaked T waves of hyperpotassemia, together with varying degrees of atrioventricular and intraventricular block, have been noted.[2-9] No unanimity of opinion with regard to the duration of the Q-T interval in hyperpotassemia has been expressed.

Prolongation of the Q-T interval has been long associated with hypocalcemia,[10-13] and several times it has been stated that this prolongation occurs in the RS-T segment.[4,14] In a few instances shortening of the Q-T interval has been demonstrated with high serum calcium levels.[11,11,14]

Suggestive evidence has been produced that reversible electrocardiographic changes may be associated with fluctuations in serum electrolytes other than potassium and calcium.[5,15,16] Changes in blood pH accompanying hyperventilation[15,16] or sodium bicarbonate or ammonium chloride ingestion[15] have been correlated with the amplitude of the T wave in the standard electrocardiographic leads. In these experiments, however, variations in myocardial blood supply or changes in ionized calcium or in heart position could not be excluded as significant factors. Animal experiments indicate that magnesium may have some depressive effect upon the conduction system when the serum level is elevated to several times its normal value.[20] Injection of relatively large amounts in man, however, has been shown to be without significant effect on the electrocardiogram.[21]

In this study we have empirically related serum electrolyte concentrations and electrocardiographic repolarization wave patterns in a large number of cases. It is our purpose (1) to confirm and elaborate on previously noted phenomena primarily with regard to calcium and potassium and (2) to attempt to demonstrate at what "critical" serum concentration of these electrolytes regularly recognizable electrocardiographic abnormalities become apparent.

MATERIAL AND METHODS

The material for this paper consisted of 141 electrocardiograms taken on seventy-eight patients. They were considered suitable for the purposes of this

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study when a more or less complete study of serum electrolytes (usually potassium, sodium, calcium, carbon dioxide combining power, chlorides, nonprotein nitrogen, and occasionally magnesium) had been made within a few hours of the taking of the electrocardiogram. Cases were discarded in which there was any reason to suspect that the presence of heart disease might have altered the form of the electrocardiogram. If digitalis or quinidine had been administered, the electrocardiograms were not included. Several of the patients had had numerous electrocardiograms and electrolyte surveys, so to avoid weighting of the material, no more than three sets of determinations on any one patient were used.

Electrocardiographic measurements were made by two different observers, and the results were averaged. Most of the electrocardiograms had precordial leads, and as far as possible measurements were made in the left ventricular lead with the largest deflection (usually V_4 or CF_4). Q-T and R-R intervals were determined on the same cycle. U-wave widths were not included in the Q-T duration but were recorded separately. T-wave heights were expressed as a percentage of the R-wave height in the same lead (to obviate variations in standardization and chest wall thickness).

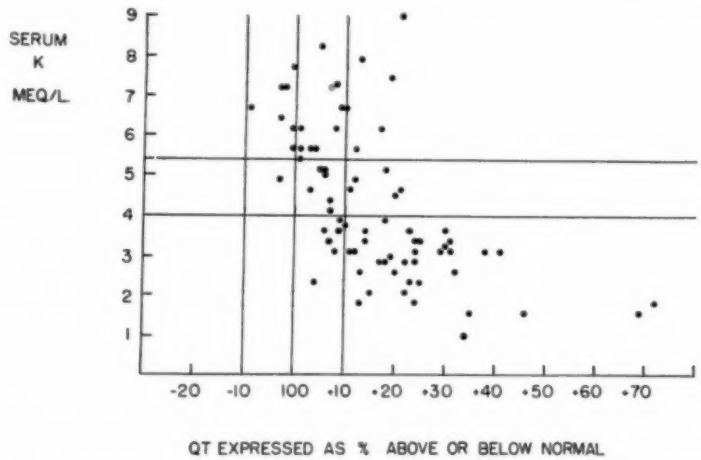

Fig. 1.—Relation of the serum potassium level to the Q-T interval of the electrocardiogram in patients with serum calcium over 4.0 meq. per liter. The two horizontal lines include the normal range of serum potassium (4.0 to 5.3 meq. per liter), and the two vertical lines include the variation in Q-T interval considered to be within the normal range.

Each observed Q-T interval was compared with the maximum expected normal for the rate in question. The expected normal was calculated from Bazett's formula[17] Q-T = K R-R, using his values for K (0.37 for adult males and children and 0.40 for adult females). The observed Q-T was expressed as a percentage above or below the expected normal.

Serum potassium and sodium levels were determined by the flame photometer.[18] The method of Simonsen and associates[19] was used for the serum magnesium estimations. Standard chemical methods were used for the determination of the serum calcium, plasma chloride, carbon dioxide combining power, and nonprotein nitrogen levels.

RESULTS

Potassium

Q-T Interval.—In seventy-seven instances (forty-six patients) there were measurements of serum potassium with the serum calcium known to be or presumed to be* within relatively normal limits (above 4.0 meq. per liter) (Fig. 1). The diagnoses on these forty-six patients are listed in Table I.

TABLE I. DIAGNOSES OF THE PATIENTS FROM WHOM THE DATA PRESENTED IN FIG. 1 WERE OBTAINED

DIAGNOSIS	NUMBER OF PATIENTS
Diabetic acidosis	10
Lower nephron nephrosis	10
Postoperative complications	5
Pancreatitis	5
Chronic nephritis	4
Pyloric obstruction	3
Fecal fistula	2
Periodic paralysis	1
Intestinal obstruction	1
Addison's disease	1
Ruptured appendix	1
Tubular acidosis	1
Lupus erythematosus	1
Gastric crisis	1

It will be seen (Fig. 1) that when the potassium level was below 4.0 meq. per liter, the Q-T interval was usually (but not always) more than 10 per cent prolonged. The prolongation was more constant when the potassium was below 3.5 meq. per liter and quite constant at levels below 3.0 meq. per liter, only one of twenty records failing to show 10 per cent or more prolongation and thirteen of twenty showing more than 20 per cent prolongation.

Nearly all electrocardiograms associated with elevated potassium levels (over 5.3 meq. per liter) had Q-T intervals within the normal range (plus or minus 10 per cent deviation from normal). Five of twenty-three electrocardiograms showed Q-T prolongation over 10 per cent and none more than 10 per cent shortening. Minor degrees of hypocalcemia were present in most of these patients (lower nephron nephrosis), so it is possible that somewhat shorter Q-T intervals might have been expected from potassium effects alone.

In thirty-five records of patients with a known potassium level and significant hypocalcemia (under 4.0 meq. per liter), the Q-T interval was prolonged more than 10 per cent in thirty-one instances irrespective of the level of potassium (Fig. 2).

T Wave.—A fairly close relationship between the height of the left ventricular T wave and the serum potassium level is evident (Fig. 3). On 105 occasions in seventy-one patients the serum potassium level was known and the T-wave height was measurable in a left ventricular precordial lead of the electrocardio-

*In a few cases calcium measurements were not made on the same day.

gram. These patients include those listed in Table II as well as all those in Table I. Serum calcium levels were disregarded except in three cases in which it was felt that peculiar late T-wave inversion might have been due to severe hypocalcemia. These three cases were excluded.

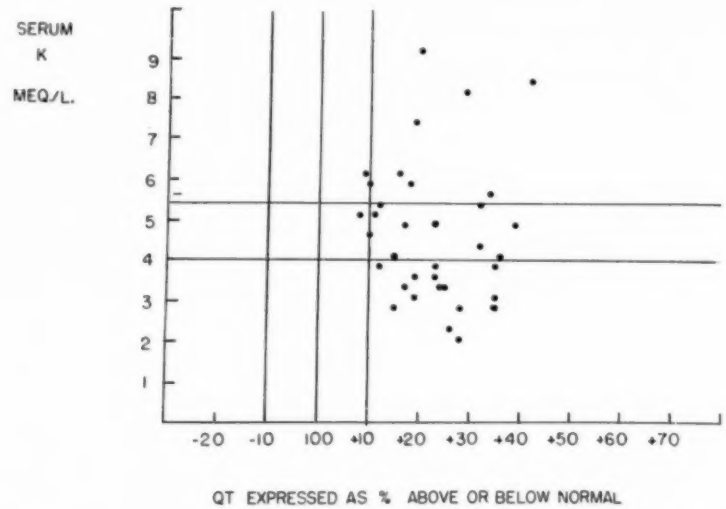

Fig. 2.—Relation of the serum potassium level to the Q-T interval of the electrocardiogram in patients with serum calcium under 4.0 meq. per liter. Horizontal and vertical lines are the same as in Fig. 1.

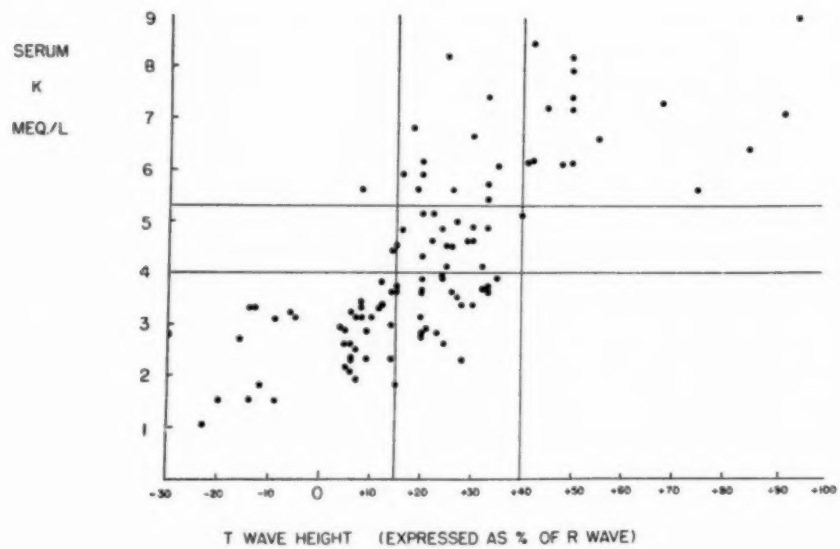

Fig. 3.—Relation of the serum potassium level to the height of the left ventricular T wave in patients with varying serum calcium levels. The two horizontal lines include the normal range of serum potassium (4.0 to 5.3 meq. per liter), and the two vertical lines include the approximate normal range of T-wave height expressed as a percentage of the R-wave height in the same lead.

TABLE II. DIAGNOSES OF SOME OF THE PATIENTS FROM WHOM THE DATA PRESENTED IN FIG. 3 WERE OBTAINED*

DIAGNOSIS	NUMBER OF PATIENTS
Postoperative complications	5
Cancer of stomach	3
Chronic nephritis	2
Pancreatitis	2
Diarrhea	2
Diabetic acidosis	1
Lower nephron nephrosis	1
Tuberculosis	1
Myeloma	1
Vomiting; unknown cause	1
Hypoparathyroidism	1
Pulmonary emphysema	1
Peptic ulcer, perforated	1
Peptic ulcer, bleeding	1
Septicemia	1
Pyloric obstruction	1

*The diagnoses of the remainder of this group of patients appear in Table I.

In a left ventricular precordial lead the normal T wave is usually between 15 and 40 per cent of the height of R. It will be seen (Fig. 3) that in those cases with unusually tall T waves (more than 40 per cent of R) the serum potassium was elevated in every instance. However, five patients with considerable serum potassium elevation (over 6.0 meq. per liter) failed to demonstrate T waves outside the normal range.

In contrast it is evident that in most of the instances where the T wave was of unusually low amplitude (less than 15 per cent of R), the serum potassium level was below normal. However, a considerable number of patients with serum potassium levels below 4.0 meq. per liter had T waves within the normal range, and it was not until a level of 3.0 meq. per liter or below was reached that the T wave was affected with any regularity. Here, too, in seven instances out of twenty-seven the T wave could still be considered to be within the low normal range. Even at serum levels below 2.5 meq. per liter the T wave was occasionally 15 per cent or more of the R wave (two instances). Inverted T waves were usually associated with depressed or sagging ST segments, and they often had a characteristic appearance because of associated Q-T prolongation. Rarely, but occasionally, the T-wave inversion resembled that of the pattern of left ventricular hypertrophy (Fig. 5). In addition to a decrease in T-wave height some broadening of the base was often noted with low serum potassium levels.

The T waves associated with hyperpotassemia were nearly always peaked in appearance with symmetrical ascending and descending limbs. This may not be true with extremely high serum potassium levels. None above 8.8 meq. per liter were seen in this series.

RS-T Segment.—With low potassium levels the RS-T segment appeared to increase in length proportionately to the Q-T interval.

U Wave.—There was an unusually high incidence of U waves associated with hypopotassemia (55 per cent of all cases below 4.0 meq. per liter). In contrast only 7 per cent of the tracings associated with serum potassium over 4.0 meq. per liter exhibited a U wave. With potassium levels below 3.0 meq. per liter the U waves were frequently large (35 per cent of all cases). Inclusion of this broad U wave in the Q-T interval would considerably increase the Q-T abnormality, and it is to be noted that, if the standard leads are used for the measurement of Q-T, the U wave will often be included in the measurement since in these leads it may be indistinguishable from the T waves.

Conduction Defects.—In this series there was a low incidence of appreciably delayed auriculoventricular or intraventricular conduction times accompanying abnormal potassium levels (potassium below 3.0 meq. per liter, two instances; potassium above 6.0 meq. per liter, three instances).

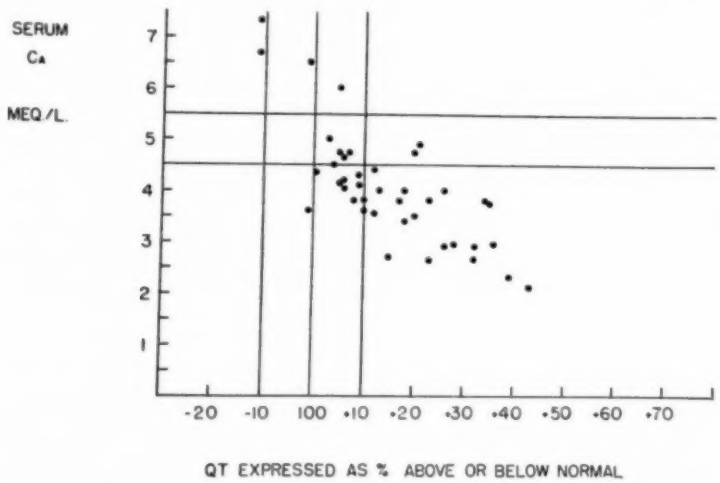

Fig. 4.—Relation of the serum calcium level to the Q-T interval of the electrocardiogram in patients with normal serum potassium levels (4.0 to 5.3 meq. per liter). The two horizontal lines include the normal range of serum calcium (4.5 to 5.5 meq. per liter), and the two vertical lines include the variation in the Q-T interval considered to be within the normal range.

Conclusions.—

1. With moderately low potassium levels (under 4.0 meq. per liter) the Q-T interval tends to be prolonged, but not with sufficient regularity to be diagnostic.

2. With levels of potassium below 3.0 meq. per liter the Q-T interval is quite regularly prolonged, usually in proportion to the potassium deficiency, but rarely more than 40 per cent beyond the normal.

3. In this series neither prolongation nor shortening of Q-T was observed with any regularity in hyperpotassemia. Minor degrees of hypocalcemia in some instances may have counteracted possible shortening effects of elevated potassium.

4. Hypocalcemia caused Q-T prolongation irrespective of the level of potassium.

5. There is an increased incidence of U waves in hypopotassemia. These may interfere with the accurate measurement of Q-T if the standard leads are used.

6. The T wave is usually decreased in height (less than 15 per cent of the R wave) or inverted when the serum potassium is below 3.0 meq. per liter.

7. The T wave is quite consistently increased in height (more than 40 per cent of R) when the serum potassium is above 6.0 meq. per liter and is usually peaked in appearance.

TABLE III. DIAGNOSES OF THE PATIENTS FROM WHOM THE DATA PRESENTED IN FIG. 4 WERE OBTAINED

DIAGNOSIS	NUMBER OF PATIENTS
Hypoparathyroidism	6
Lower nephron nephrosis	5
Diabetic acidosis	4
Chronic nephritis	3
Hyperparathyroidism	2
Pancreatitis	2
Metastatic carcinoma	2
Postoperative complications	2
Gastric carcinoma	1
Amyloid nephrosis	1
Tubular acidosis	1
Pyelonephritis	1
Myeloma	1

Calcium

Q-T Interval.—In forty-one instances (thirty-one patients) there were calcium measurements with concurrently normal potassium levels (Fig. 4). The diagnoses of these patients are listed in Table III. With calcium levels under 4.0 meq. per liter the Q-T interval was usually more than 10 per cent prolonged (eighteen of twenty-three cases). With levels under 3.5 meq. per liter the Q-T was prolonged in all cases and usually more than 20 per cent.

The prolongation appeared to be predominantly in the RS-T segment in the majority of instances. In 68 per cent of the records of patients with calcium under 3.5 meq. per liter the RS-T segment composed three-fifths or more of the Q-T interval (an unusually high proportion).

In patients with hyperpotassemia and calcium levels under 4.0 meq. per liter, the Q-T was usually prolonged (Fig. 2).

In two of the four patients with hypercalcemia the Q-T was unusually short due to a marked decrease in length of the RS-T segment. The T wave did not appear to decrease in width appreciably in these electrocardiograms.

T Wave.—In most instances the T wave did not appear to be affected by the serum calcium level. In three patients, however, with serious calcium deficits there was sharp, late T-wave inversion of unusual character and unexplained cause (not associated with potassium deficit). The significance of this finding is undetermined and will be investigated.

U Wave.—No relation between calcium fluctuations and the appearance of U waves was noted.

Conduction Defects.—No conduction defects were noted in association with abnormal serum calcium levels.

Conclusions.—

1. Calcium levels below 4.0 meq. per liter usually prolong the Q-T interval significantly; this is nearly always true when the level falls below 3.5 meq. per liter. The magnitude of this prolongation is generally somewhat greater than with potassium deficiencies of a like degree.

2. The prolongation of the Q-T is largely in the RS-T segment rather than in the T wave.

3. Hypercalcemia appears to shorten the Q-T interval, also acting chiefly on the RS-T segment. The amount of shortening may be limited by the breadth of the T wave which does not appear to decrease.

4. Except in three isolated instances, the T wave did not appear to be appreciably affected by calcium levels.

Other Electrolytes

A number of abnormal magnesium determinations (both high and low) were discovered in this series with no apparent electrocardiographic correlation. However, the data are insufficient for a definite conclusion in this regard.

No evidence was elicited that changes in sodium or chloride concentration or elevation of the nonprotein nitrogen exerted any recognizable influence on the electrocardiogram.

No correlation was recognized between the level of the carbon dioxide combining power and the height of the T wave. Changes in the latter that were associated with abnormal carbon dioxide levels could usually be related to potassium variations. In a few instances, with marked depression of the carbon dioxide combining power (diabetic acidosis), there was an unusual shape to the ST segment and ascending limb of the T wave. The significance of this finding has not been determined.

Insufficient determinations of blood pH were done to draw any definite conclusions regarding hydrogen-ion concentration.

DISCUSSION

In addition to the static changes seen in these electrocardiograms, restoration of the abnormal measurements to normal was frequently noted, associated with correction of the electrolyte disturbance. An example is illustrated in the electrocardiogram of a 17-year-old boy with chronic nephritis (Fig. 5) taken during the active correction of severe serum potassium and calcium deficits. In the original electrocardiogram it will be seen that V_5 somewhat resembled the pattern of left ventricular hypertrophy, though the Q-T interval was unusually long, and a U wave was visible. With restoration of the serum potassium to normal the T-wave abnormality disappeared and the U wave diminished in size, though the Q-T interval did not change. Partial restoration of the serum calcium to normal then slowed the rate and shortened the Q-T interval.

Of the combinations of abnormalities of potassium and calcium the commonest are (1) low calcium and high potassium (uremia) and (2) low calcium and low potassium. The first of these combinations is usually recognizable, while the second may offer some difficulty in interpretation. We have not seen combinations of high calcium and low potassium or high calcium and high potassium.

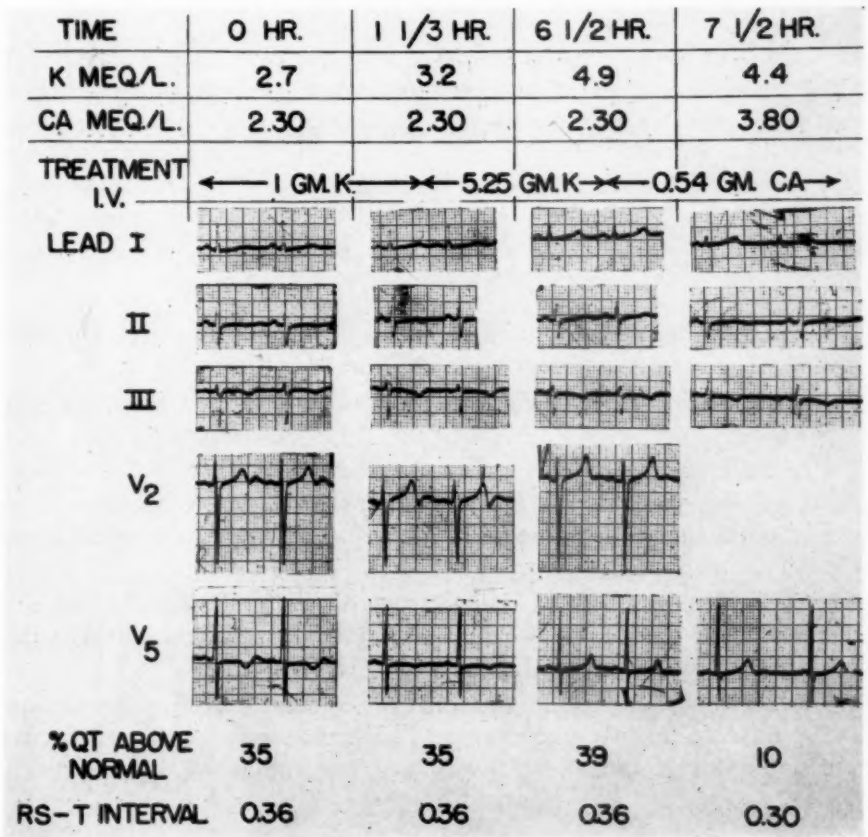

Fig. 5.—Electrocardiograms made during the correction of severe serum potassium and calcium deficits on a patient with chronic nephritis and uremia.

Though the patterns of abnormal serum calcium and potassium seem relatively specific, the authors wish to emphasize that they have seen identical patterns in the electrocardiograms of patients with heart disease and normal serum electrolytes. Likewise, abnormal serum calcium and potassium levels can exist, on occasion, without the characteristic electrocardiographic changes. This is particularly true with regard to potassium, and such instances were encountered in this series. Others[22] have presented examples in which the electrocardiogram did not correlate with the serum potassium level. The fundamental question as to the relative importance of the serum and intracellular electrolyte levels in determining the form of the electrocardiogram is raised and cannot be answered at this time.

In spite of these facts, the data indicate that the correlation between abnormal serum levels of calcium and potassium and the electrocardiographic changes is suggestive, particularly with values of calcium and potassium above or below the listed "critical" levels. In the case of potassium, if it is really the intracellular level that determines the form of the electrocardiogram, then the data merely indicate that the serum level is usually a dependable index of the intracellular level.

Because of the difficulties encountered in an exact measurement of the Q-T interval (particularly with rapid heart rates) and because of the empiricism attached to the various formulas for rate correction of Q-T, the authors feel that too much significance should not be given to minor variations of this measurement from the calculated "normal." For this reason, we have regarded as significant only those values which deviated more than plus or minus 10 per cent from the expected "normal."

SUMMARY

1. Variations in potassium and calcium appear to be chiefly, if not entirely, responsible for electrolyte effects on the electrocardiogram.

2. These effects are mainly on the form and duration of the repolarization wave.

3. In the absence of gross changes due to heart disease, digitalis, or quinidine, a reasonably accurate prediction of marked deficits or excesses of either calcium or potassium can be made from the effects these ions produce on the electrocardiogram.

4. In the interpretation of the electrocardiogram it should be appreciated that, at least in the case of potassium, it may be the intracellular, rather than the serum, level that influences the repolarization wave.

5. Recognizable electrocardiographic abnormalities are usually present at levels of serum calcium below 3.5 meq. per liter and above 6.0 meq. per liter and at levels of serum potassium below 3.0 meq. per liter and above 6.0 meq. per liter.

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EXTRACARDIAC ARTERIOVENOUS FISTULAS IN THE THORAX

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ARTERIOVENOUS communications within the chest are frequently revealed by pathognomonic physical findings. Yet occasionally their presence may be overlooked and the condition misdiagnosed because of unfamiliarity with the complex clinical manifestations which they may present. A knowledge of the altered circulatory dynamics of such lesions is essential for their recognition and management.

Characteristic syndromes have been described for communications between the aorta and various chambers of the heart,[1] usually the result of aneurysmal rupture. Intracardiac communications can usually be recognized by careful clinical study, and they can now be confirmed by the newer techniques of angiocardiography and catheterization. Extracardiac fistulas between the vessels within the chest cavity have within recent years offered more possibilities for surgical cure. Thus, early recognition and localization of such lesions is desirable before further complications occur.

From the theoretical standpoint, there are five different types of arteriovenous communications possible within the thorax. These are communications from the aorta to the pulmonary artery, aorta or peripheral artery to a systemic vein, pulmonary artery to the pulmonary vein, aorta to the pulmonary vein, and pulmonary artery to a systemic vein.

Within the past year, we have studied at the University of Texas Hospitals one of each of the first three types. Each case is sufficiently unusual to merit a separate report. However, since they fall under this same general group, we wish to present them together in order to emphasize the salient clinical features in the light of the circulatory dynamics involved.

AORTA TO PULMONARY ARTERY

Communications between the aorta and the pulmonary artery are usually congenital in origin, resulting from persistence of the ductus arteriosus, which normally closes by three months after birth. Originally described by Botallus (1530), this anomaly is one of the most common of congenital defects and is amenable to correction.

That such a communication can be an acquired lesion, resulting from rupture of the dilated aorta into the pulmonary artery, has been known since the report of

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Hope[2] in 1842. Sporadic case reports followed, summarized by Peacock[3] in 1868. In 1907, Kappis[4] reviewed the previously reported cases, thirty-two in number, and added one of his own. Scott,[5] in 1924, and Porter,[6] in 1942, described other cases.

The syndrome of the rupture of an aortic aneurysm into the pulmonary artery has been well delineated. Before the rupture takes place, there may be preliminary pressure on the pulmonary artery, causing stenosis with premonitory symptoms and signs. The actual rupture usually produces severe pain, but this may be overshadowed by other symptoms such as collapse or shock. The severity of the symptoms depends upon the size of the fistula and pressure effects on other mediastinal structures. Severe dyspnea is a prominent feature and tends to be progressive. There then follow the symptoms of right heart failure.

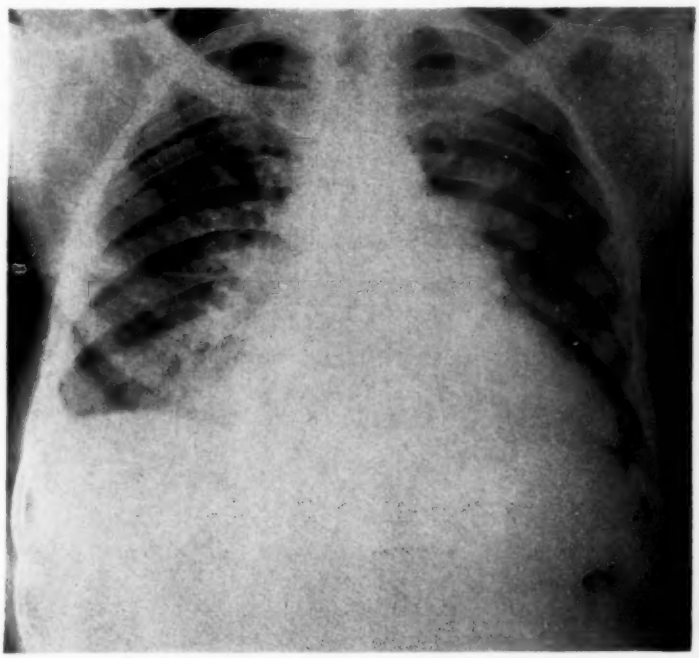


Fig. 1.—Posteroanterior film of the chest (Case 1) demonstrates cardiac enlargement with prominence of the pulmonary conus. There are congestive changes in the lungs, with fluid at the right base.

Prominent diagnostic signs make their appearance. These depend on the size of the aneurysm, the size and location of the opening, and the pressure differences between the two vessels. A continuous thrill, with systolic accentuation, is palpable over the second or third intercostal space to the left of the sternum. The corresponding murmur is usually loud and harsh and accentuated in systole. The second pulmonic sound is strikingly augmented. Peripheral signs similar to those in free aortic insufficiency are present. There appear the signs of striking and intractable right ventricular overload and failure. The course is usually rapidly downhill, with death in a few weeks to months.

The following case is remarkable for the unusually long survival in spite of severe congestive failure.

CASE 1.—W. T., a 38-year-old Negro man, was admitted to the hospital on Sept. 21, 1949, with complaints of dyspnea, dull abdominal pain, and bilateral leg edema. The symptoms began six weeks previously, at which time he suffered a sharp, constricting, substernal pain that radiated

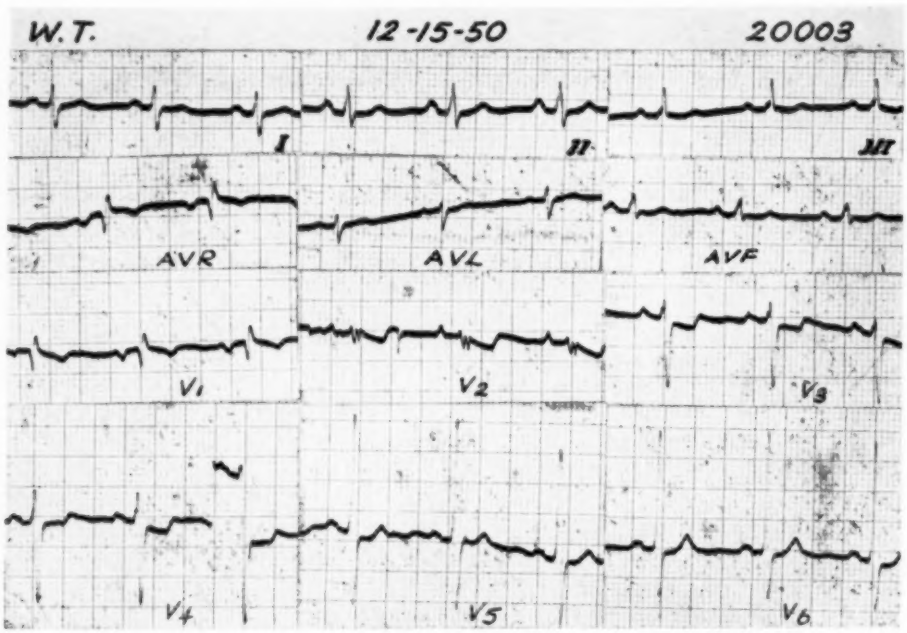


Fig. 2.—The electrocardiogram (Case 1) shows right axis deviation with right ventricular hypertrophy.

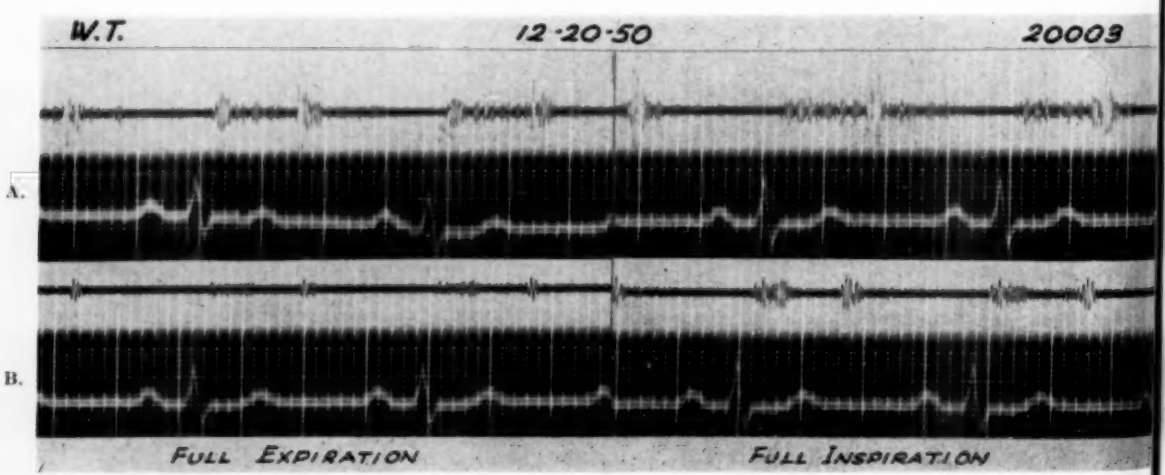


Fig. 3.—The phonocardiogram (Case 1) demonstrates the continuous murmur with systolic accentuation and loud P_2, heard best slightly left of the pulmonic area. The intensity of the murmur is increased on deep inspiration. *A*, Second intercostal space 4 cm. left of the mid-sternal line; *B*, tricuspid area.

posteriorly to the level of the second thoracic spine and persisted for several hours. He coughed up a small quantity of blood and developed a low-grade fever. A diagnosis of pneumonia was made by the local physician, and he was treated with penicillin. A week later, there developed dyspnea, abdominal distention, pain in the right upper quadrant, and swelling of both legs. He was digitalized and showed temporary improvement. However, after several days, he developed paroxysmal nocturnal dyspnea, orthopnea, and increasing edema, which persisted until he came to the hospital. The past history was noncontributory.

Physical examination revealed an orthopneic, hyposthenic man in moderate respiratory distress, with temperature of 98.6° F., pulse 106, blood pressure 130/55 mm. Hg bilaterally, and respirations 26. The abdomen was protuberant, and the legs were edematous. The pulse was of the water-hammer type, capillary pulsations were demonstrable, and Duroziez's sign was present. The neck showed prominent pulsations, but no tracheal tug was felt. Dullness was present at both lung bases, over which moist râles were heard. The apical cardiac impulse was in the sixth intercostal space in the anterior axillary line, and percussion of the cardiac outline showed enlargement to the left. A systolic thrill was felt in the second and third intercostal spaces to the left of the sternum. Over this area was heard a loud, continuous, harsh machinery murmur with systolic accentuation, maximal in the second intercostal space 4 cm. to the left of the mid-sternal line. The pulmonic second sound was markedly accentuated. The abdomen revealed shifting dullness, and a fluid wave was present. The liver was moderately tender and enlarged, extending 4 cm. below the right costal margin. There was a bilateral pitting edema to the level of the knees. The blood serology was positive for syphilis. The hemogram and the blood chemistry findings were normal.

The venous pressure was 24 cm. of saline, and circulation time with magnesium sulfate was 60 seconds. A posteroanterior film of the chest (Fig. 1) showed cardiac enlargement with particular prominence of the pulmonary conus region. Pulmonary congestion with fluid in the right hemithorax was also demonstrated. The electrocardiogram (Fig. 2) showed right axis deviation, right ventricular hypertrophy, and clockwise rotation on the longitudinal axis. A phonocardiogram (Fig. 3) confirmed the auscultatory findings, showing that the intensity of the murmur was increased on deep inspiration.

Clinical Course.—The patient responded satisfactorily to a regime consisting of bed rest, sodium restriction, digitalization, and Thiomerin. He was discharged one month after admission and was followed as an outpatient. After readmission on Jan. 1, 1950, because of recurrence of cardiac decompensation, intracardiac catheterization was done.* The results (Table I) confirm the existence of a shunt from the aorta to the pulmonary artery. Aqueous penicillin in doses of 50,000 units each three hours was given for seven days (total 2.8 million units), and later Crysticillin, 300,000 units, was given twice daily for fifteen days (total 9 million units) as antisyphilitic therapy. The patient has now been followed at frequent intervals for seventeen months. Many thoracenteses and abdominal paracenteses have been necessary because of the intractable right ventricular failure. He is still alive.

TABLE I. RESULTS OF CATHETERIZATION STUDY

	SUPERIOR VENA CAVA	RIGHT ATRIUM	RIGHT VENTRICLE	MAIN PULMONARY ARTERY
Mean Pressure (mm. Hg)	18.3	13.2	34.0	48.0
Oxygen Content (vol. per cent)	9.70	9.54	8.91	14.54

Comment.—The clinical diagnosis of communication between the aorta and pulmonary artery was made by each of the authors independently. This was presumably the result of rupture of a syphilitic aneurysm of the aorta. There

*By Dr. S. Y. Tsai.

was no clinical evidence of a bacterial endocarditis, previous examinations before onset of symptoms had revealed no murmur, and the patient himself had been aware of no bruit until after the onset of the pain. Thus, the possibility of a patent ductus arteriosus with perhaps further erosion due to a superimposed bacterial endocarditis would appear to be ruled out. The rupture of the aorta into the pulmonary artery apparently occurred at the time of the severe, constricting precordial pain seventeen months previously. This was followed by a syndrome of chronic severe right ventricular failure. The peripheral findings and intensity of the murmur and thrill would indicate an extensive communication. This condition carries a very poor prognosis and is usually fatal within a few months. The survival of this patient is surprising in view of the persistent conspicuous cardiac failure.

AORTA TO SUPERIOR VENA CAVA

Beavor[7] is generally given credit for reporting in 1832 the first case of perforation of an aortic aneurysm into the superior vena cava. The diagnostic characteristics of the syndrome were set down in 1890 by Pepper and Griffith.[8] Armstrong and associates,[9] in 1939, reaffirmed the clinical symptoms and diagnostic signs in analyzing 192 cases in the literature, with the addition of two of their own.

The symptoms are usually sudden and dramatic in onset, with the development of a superior vena caval obstruction syndrome consisting of cyanosis, edema, and venous distention of the upper one-half of the body. The presence of a pulsating tumor in the thorax can be detected by physical and radiological means. The differentiation between this and the conditions causing superior vena caval obstruction is the frequent presence of a characteristic harsh continuous murmur with systolic accentuation, which may be accompanied by a thrill usually felt only in systole. Pulsations in the veins of the neck may serve as a clue to the diagnosis. The peripheral circulatory findings are similar to those found in free aortic regurgitation.

The characteristic murmur is not always present and may be modified by variations in size of the communication and by interference through the great edema of the thoracic walls. The coexistence of aortic insufficiency or other valvular disease may confuse the clinical findings.

The following case presented the typical diagnostic clinical features, which made possible an ante-mortem diagnosis. Positive oscillations, while the venous pressure in the arms was being taken, and oxygen content studies of venous blood in the upper and lower extremities confirmed the diagnosis before death.

CASE 2.—S. R., a 45-year-old Mexican man, was admitted to the hospital on Nov. 20, 1950, with the complaint of severe, intermittent substernal pain of six months' duration. Hoarseness had been present for approximately twelve months. About six months prior to admission he suffered a severe, constricting pain in the right upper chest which radiated to the right shoulder. This was followed by an episode of hematemesis, productive of one-half cup of blood. He then noted progressive swelling of the right arm, face, and neck. Past history disclosed that twenty years previously he had had a hard chancre, and eight years afterward he was treated with several intramuscular injections. During the past six years there had been occasional attacks of orthopnea.

Examination (Fig. 4) revealed an orthopneic male in acute distress, complaining of pain in the right upper side of the chest. The blood pressure was 142/60 mm. Hg (left) and 150/55 mm. Hg (right), temperature 101° F., pulse 72, and respirations 20. There were cyanosis and marked edema of the right upper extremity and neck and, to a lesser degree, of the left arm. Numerous small petechiae were present on the right arm. There was a slight prominence of the right upper chest, and a tracheal tug was elicited. Positive venous pulsations were noted in the neck, and the superficial veins of the chest were conspicuously dilated. An active apical cardiac impulse was felt at the fifth intercostal space slightly outside the mid-clavicular line, and the left border of cardiac dullness was displaced to the left. There was dullness to percussion of the entire right upper chest anteriorly, extending into the right axilla. On auscultation there was heard a continuous high-pitched musical murmur with systolic accentuation in the right first intercostal space, just outside the mid-clavicular line. A rough systolic murmur and a high-pitched decrescendo diastolic murmur were heard at the aortic area, the latter being transmitted unchanged in character to the apex. Breath and voice sounds were absent in the right upper chest anteriorly.

Fig. 4.—Photograph (Case 2) shows the edema of the upper one-half of the body and markedly dilated collateral veins of the thorax.

Examination of the abdomen, lower extremities, and neurological system revealed all to be within normal limits. The blood serology was positive for syphilis. The hemogram was normal, except for a slight neutrophilic leucocytosis. The urine contained a trace of albumin, rare granular casts, and two to five erythrocytes per high-power field. The blood chemistry findings were normal except for slightly low carbon dioxide combining power.

X-ray studies of the chest revealed a huge mass in the right anterior chest, measuring about 18 by 14 cm. on the posteroanterior film (Fig. 5). The electrocardiogram showed complete right bundle branch block and left ventricular hypertrophy. The phonocardiogram with the microphone over the right anterior chest is reproduced in Fig. 6, taken on deep expiration and deep inspiration.

Venous pressures showed marked elevation in the upper extremities, being 30 cm. in the right and left arms and 17 cm. in the left leg. Marked pulsations of the saline column were noted when the venous pressure in the arms was taken. Oxygen content studies* in the peripheral blood confirmed the clinical diagnosis. The oxygen content was 11.46 volumes per cent in the right median cubital vein, 6.34 volumes per cent in the left median cubital vein, 5.18 volumes per cent in the right femoral vein, and 13.63 volumes per cent in the right femoral artery.

Clinical Course.—The condition of the patient became progressively worse, with increasing swelling of the upper one-half of the body and further dilatation of the superficial veins of the chest wall. Orthopnea became extreme, with continuous cough and episodes of hematemesis. He died suddenly, thirty-five days after admission.

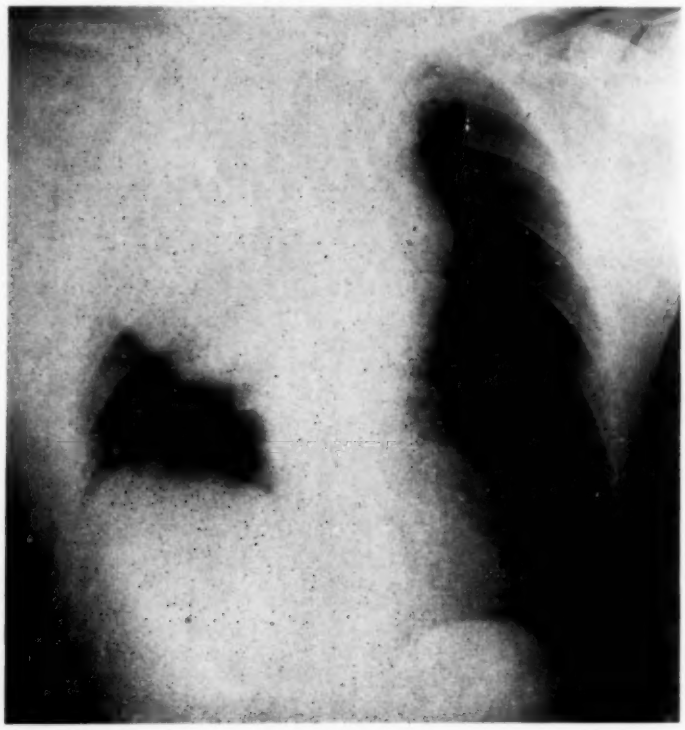


Fig. 5.—Posteroanterior film of the chest (Case 2) shows the large aneurysm of the aorta in the right upper chest.

Pertinent Post-mortem Findings.†—A large aneurysm of the aorta, 13 cm. in diameter, filled the mediastinum and extended into the right upper chest. The aortic aneurysm had ruptured into the superior vena cava (Fig. 7), producing an arteriovenous communication with a diameter of about 3 cm. Caudad to this communication, the bulge of the aneurysm encroached upon the lumen of the superior vena cava to produce partial obstruction. The wall of the ascending portion and arch of the aorta showed classical gross and microscopic findings of syphilitic aortitis, and the aortic valves were insufficient. A massive collection of blood was present in the upper gastrointestinal tract, apparently due to ruptured esophageal varices.

Comment.—This patient presented the classical findings of the syndrome of aortic rupture into the superior vena cava. The clinical diagnosis was confirmed by the presence of marked pulsations of the saline column in venous pressure determinations in the upper extremities and increased oxygen content of the

*Made by Dr. Lawrence May.

†The necropsy was done by Dr. Stanley L. Smith.

venous blood in the upper extremities, especially the right. The obstruction caudad to the arteriovenous communication probably protected the right heart from some of the burden of the increased venous return.

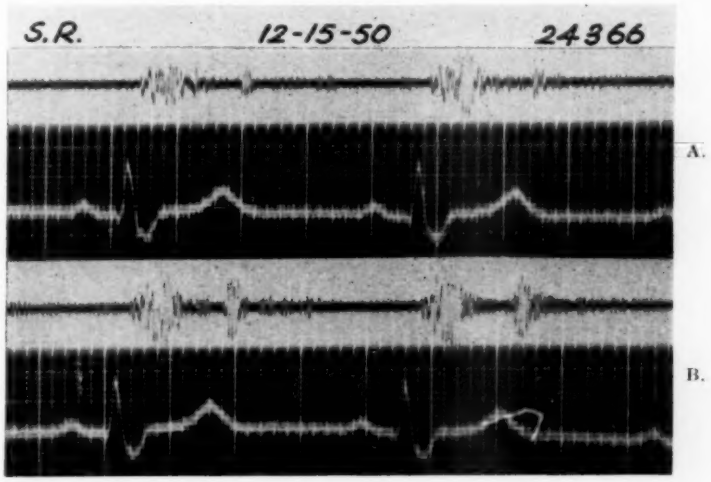


Fig. 6.—A phonocardiogram (Case 2) taken over the arteriovenous fistula shows a continuous murmur with systolic accentuation. This murmur is intensified on deep inspiration. *A*, Expiration; *B*, inspiration.

PULMONARY ARTERY TO PULMONARY VEIN

Pulmonary arteriovenous fistulas are of congenital, and often familial, origin. Most significantly, when recognized, they can be cured surgically, even when multiple. The first description of the condition was by Churton[10] at necropsy in 1897. The association of the condition with the triad of cyanosis, polycythemia, and clubbing was emphasized by Reading[11] in 1932. Moyer and Ackerman[12] pointed out the frequent relationship of pulmonary hemangiomas to hereditary hemorrhagic telangiectasia. Smith and Horton[13] made the first clinical diagnosis in 1939, and Hepburn and Dauphinee,[14] in 1942, reported the first pneumonectomy for the condition. Yater and associates,[15] in 1949, collected a series of forty-five cases, of which two were their own, and in this group surgical treatment had been employed in twenty-four. Since Yater's report, at least fifteen cases have been reported,[16-20] of which eight were treated surgically (see Addendum).

Bacterial complications have been infrequent and have been successfully treated. In two cases death occurred due to brain abscess.[11,21] Maier and co-workers,[22] in 1948, reported the only previous case similar to ours in that it was complicated by subacute bacterial endarteritis, which responded to antibiotics and then was cured by lobectomy.

The cardinal diagnostic signs are cyanosis, polycythemia, and clubbing, with normal heart and spleen; it is associated with murmurs which may be near the heart but are definitely extracardiac. The associated occurrence of telangiectases in the skin and mucous membranes was a valuable diagnostic aid in about one-half the cases. Usually a murmur can be heard over the chest outside the precordium, with the point of maximal intensity near the site of the lesion. This murmur is typically continuous, with maximal intensity in late systole and early

diastole, but it has been noted that occasionally only the systolic component can be heard. Pulmonary hemangiomas may occur singly, but are frequently multiple.

The blood pressure is usually within normal limits. The heart is not enlarged. The electrocardiogram is usually normal.

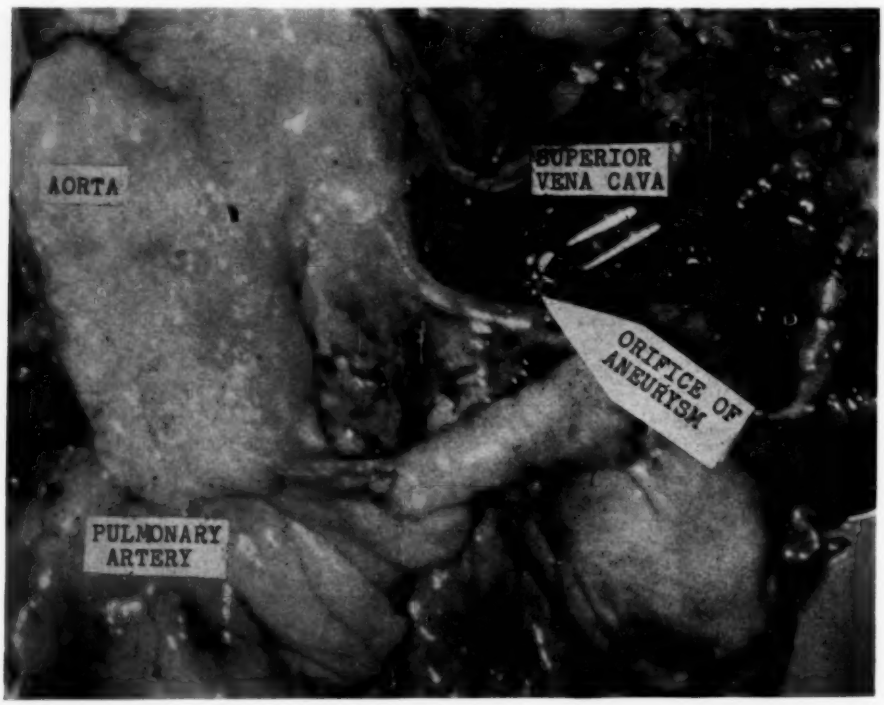
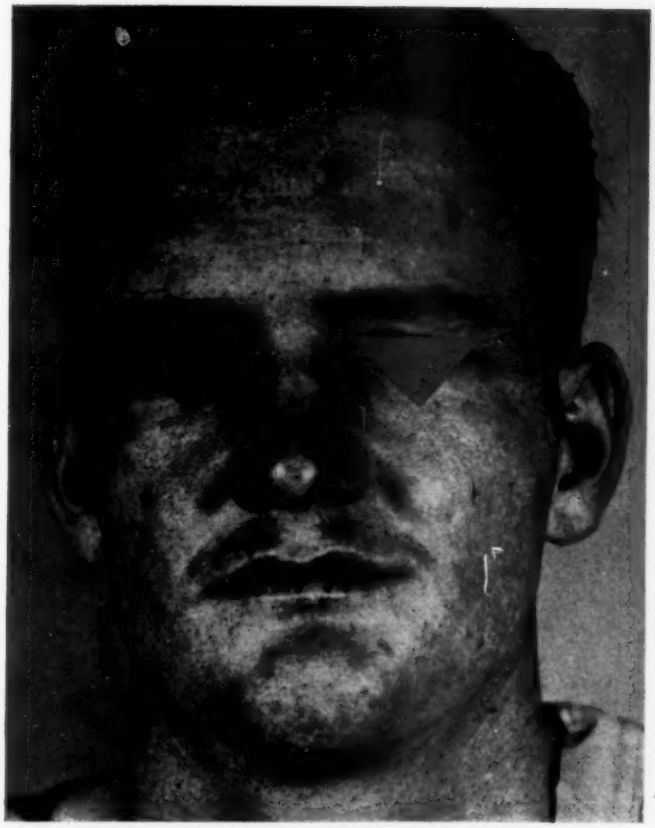


Fig. 7.—In the post-mortem specimen (Case 2), an arrow denotes the communication between the aortic aneurysm and the superior vena cava. The forceps passes from the origin of the superior vena cava directly into the orifice of the arteriovenous fistula.

The radiological features in these cases are characteristic and have been well described by Lindgren.[23] Circumscribed and slightly lobulated shadows of increased density are noted in the lungs, and these are connected with the hilar vessels by tortuous bands of increased density representing dilated branches of the pulmonary vessels. Smaller lesions may be missed on the x-ray film and discovered only at exploratory thoracotomy. Fluoroscopy demonstrates pulsations of the density, with variations in the size of the tumor, depending on intrathoracic pressure. The tumor is smaller with the Valsalva test and larger with the Mueller maneuver. Angiocardiography is a valuable diagnostic aid,[12,15,24] but it sometimes fails.[18] One death has been reported due to an iodine reaction.[25]

The present case was independently diagnosed by each of us on clinical grounds. It represents the second reported case of pulmonary hemangioma with a superimposed subacute bacterial endarteritis. This complication was diagnosed clinically, proved by culture, and subsequently cured by penicillin before operation.



A.

B.

Fig. 8.—Photographs (*A* and *B*) in Case 3 demonstrate the numerous telangiectases on the skin and mucous membranes. There is cyanosis of the ears, nose, and fingers and marked clubbing of the fingers.

CASE 3.—G. M., a 24-year-old white man, was admitted to the hospital on Dec. 8, 1950, with the complaints of general malaise, fever, and mild dyspnea for three weeks. He had been suspected of having an upper respiratory infection by his local physician, for which Chloromycetin and penicillin had been administered for five days to no avail. The past history revealed cyanosis and clubbing of the fingers since early childhood. However, he had been able to carry on normal activities without difficulty, including strenuous oil field work for the past six years. For many years he had suffered from frequent epistaxes and easily bleeding gums. In 1943, he had been rejected for military service because of a lesion of the right lung demonstrated on radiograms, for which he had been hospitalized in a sanatorium for three months. Family history disclosed that the mother, a brother, and two maternal uncles had had numerous small purple spots on the face and lips, but none of the relatives had cyanosis or clubbing.

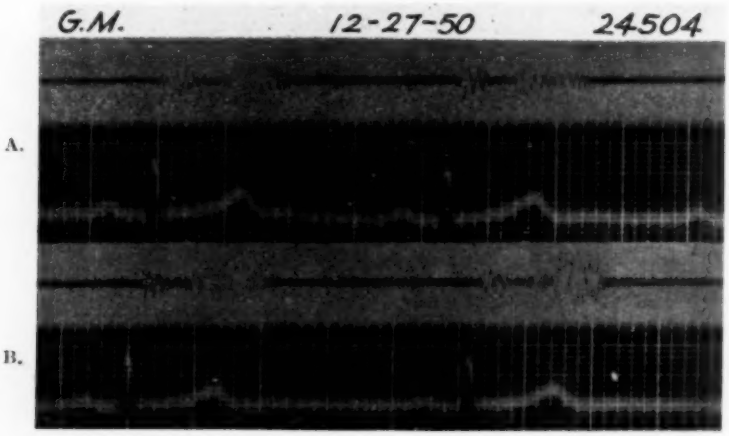


Fig. 9.—Phonocardiogram (Case 3) taken in the third intercostal space, slightly inside the midclavicular line. The continuous murmur shows accentuation in late systole and is conspicuously augmented on deep inspiration. *A*, Expiration; *B*, inspiration.

Examination (Fig. 8) revealed a cyanotic man of sthenic habitus who appeared chronically ill. The temperature was 100° F., pulse 95, respirations 20, and blood pressure 120/70 mm. Hg bilaterally. There was marked clubbing of the fingers and toes. Numerous small petechiae were noted in the conjunctivas and on the skin of the hands, and splinter hemorrhages were present under the nails. Small telangiectases were present on the lips, in the mucous membrane of the mouth, and over the face and chest. Pulsation was observed in the suprasternal notch, and a slight pulsation was visible in the third right intercostal space about 4 cm. from the mid-sternal line. A systolic thrill could be felt over this area of pulsation. Percussion of the chest revealed impairment of resonance to the right of the sternum in the second and third intercostal spaces, extending about 4 cm. to the right of the mid-sternal line. Cardiac dullness was within normal limits. Auscultation over the precordium disclosed only very distant systolic murmurs over the aortic and pulmonic areas. Over the area of dullness to the right of the sternum there was heard a harsh systolic murmur. On deep inspiration, this murmur became a continuous one, with accentuation of the systolic component and a barely audible diastolic component (Fig. 9). Examination of the abdomen and genitals was negative.

The hemogram showed a polycythemia with hemoglobin 20 Gm. per cent, erythrocytes 7.1 million, and a hematocrit of 61 volumes per cent. The urine showed a slight albuminuria and one to three erythrocytes per high-power field. Blood serology was negative and blood chemistry within normal limits. Numerous blood cultures were done before and after therapy in the hospital, and one before therapy was reported positive for *Staphylococcus albus*. X-ray films of the chest (Fig. 10) showed a somewhat irregular shadow about 5 cm. in diameter, continuous with the vascular markings in the hilar area in the posteroanterior view, situated at the base of the right lung

anteriorly. The shadow decreased on fluoroscopy with the Valsalva test and became larger with the Mueller maneuver. The electrocardiogram was within normal limits.

Clinical Course.—A diagnosis was made of pulmonary hemangioma of the right upper lobe, with complicating subacute bacterial endarteritis. The patient was treated with aqueous penicillin intramuscularly in doses of 6.4 million units per day for nineteen days, and 4.8 million units per day for the next thirty-one days. The temperature became normal on the second day of therapy and remained so for the rest of his hospitalization. No more petechiae appeared.

He was discharged following completion of therapy and readmitted three months later for surgical extirpation of the pulmonary hemangioma. At operation,* there was found a cavernous, hemangiomatous arteriovenous fistula of the right upper lobe measuring 5 by 5 by 4 cm. In addition, there were observed two smaller hemangiomas, one measuring 1 by 1 by 1 cm. in the right middle lobe and one measuring 2 by 2 by 2 cm. in the right lower lobe. Lobectomy of the right upper lobe was performed with segmental resection of the smaller hemangiomas. On the first postoperative day, the cyanosis had disappeared. Recovery was uneventful, and the patient was discharged on the tenth postoperative day. When he was seen again six weeks later, the mucous membranes were pink, and there was a notable decrease in clubbing. The red count had diminished to 4.92 million with hemoglobin 16.5 Gm. per cent.

The surgically removed right upper lobe showed a thin-walled, dilated, blood-filled space measuring 5 to 5½ cm. in diameter. Injection studies† confirmed a small arterial communication with the hemangioma and a direct communication between the lesion and the pulmonary vein draining the area. The small dissected lesions showed a similar structure.

Comment.—This is a typical case of pulmonary hemangioma, in a patient with hereditary hemorrhagic telangiectasia, with the diagnosis having been made on clinical grounds and proved at operation. It represents the second reported case with a superimposed subacute bacterial endarteritis, this complication being clinically diagnosed on the basis of fever, embolic phenomena, and positive blood culture. The bacterial infection responded to penicillin therapy. Surgical exploration later disclosed two smaller hemangiomas of the right lung in addition to the large lesion demonstrated by physical findings and roentgenogram. Response to extirpation of the lesions was most gratifying, with dramatic clearing of the cyanosis, return of the red count to normal, and a definite decrease in clubbing.

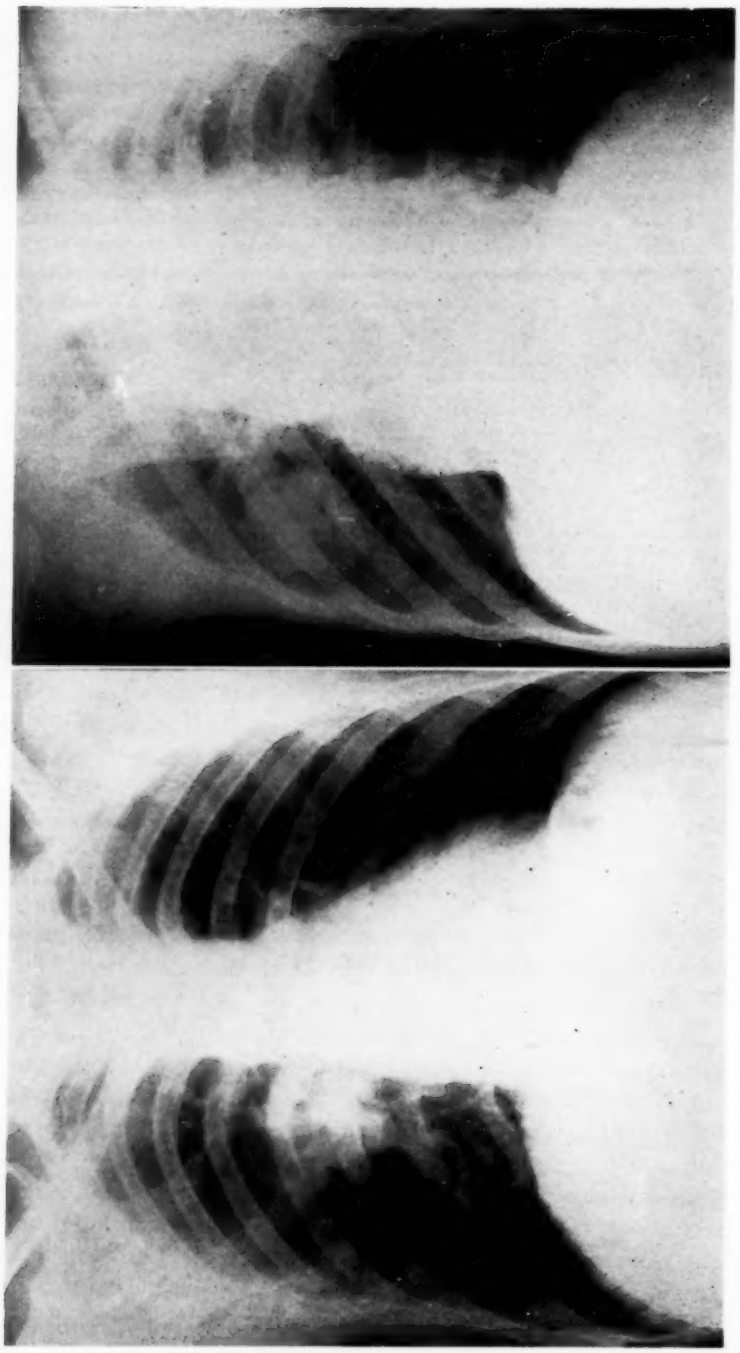
DISCUSSION

Each type of extracardiac arteriovenous aneurysm of the thorax presents a distinctive syndrome, and a diagnosis can usually be made on the basis of clinical findings. Radiological and fluoroscopic studies of the chest contribute valuable additional data. The electrocardiogram may be of value by demonstrating overload (dilatation or hypertrophy) of the cardiac chambers or may be significant in a negative manner, as in pulmonary hemangioma.

Newer techniques have been developed which are of value in confirming the clinical impression and in delineating the location and character of the lesion. Planimetry[19] has proved an effective method of study. Angiocardiography would appear to be desirable, particularly if a surgical attack is contemplated, and has been used frequently in reported cases. It does carry a small risk in patients with pulmonary hemangiomas and was not used in our case because the clear-cut clinical picture did not require it. As vascular surgery develops, it appears that more of the acquired arteriovenous fistulas will be operated upon, and visualization of the fistulas will prove most helpful to the surgeon before operation.

*Performed by Dr. A. W. Harrison.

†By Dr. J. H. Childers.



A. B.

Fig. 10.—Posteroanterior (*A*) and left anterior oblique (*B*) projections of the chest in Case 3. Note the irregular density at the base of the right lobe anteriorly which represents the pulmonary hemangioma.

Catheterization of the great veins, heart, and pulmonary artery with the recording of pressures and determination of oxygen content of blood samples from various chambers is a procedure which will frequently provide a precise diagnosis. However, it is a considerable hazard in acquired arteriovenous aneurysms because of the dangers of penetration of the catheter through a thin wall and of the possibility of dislodging thrombi. The measurements of pressure and oxygen content of blood in peripheral veins may be adequate to prove the arterial communication to a peripheral vein, as in our case of aortic rupture into the superior vena cava (Case 2).

In Case 1, the high pressures recorded by the catheter in the pulmonary artery and the increased oxygen content of pulmonary artery blood over that of the right ventricle furnish evidence of a fistula from the aorta to the pulmonary artery. The maximal normal variation of oxygen content between the superior vena cava and right atrium is 1.9 volumes per cent, between the right atrium and right ventricle 0.9 volumes per cent, between the right ventricle and pulmonary artery 0.5 volumes per cent, and within the pulmonary branches 0.4 volumes per cent.

Surgical excision has been successful in clearing the symptoms and signs of pulmonary hemangioma, but the lesions are frequently multiple. The complication of subacute bacterial endarteritis in such a lesion poses a new problem of therapy. In the previously reported case,[22] as in ours, the infection responded promptly to antibiotic therapy, and the hemangioma was subsequently extirpated. However, early surgical excision may be the procedure of choice instead of antibiotic therapy alone, just as in the generally accepted management of patent ductus arteriosus with subacute bacterial endarteritis. The advantage of early surgery would be the avoidance of embolic complications and possible spread of the organisms to other sites. Certainly if the infection does not promptly respond, early surgery is indicated. The frequent presence of multiple hemangiomas, particularly if bilateral, may make it difficult to localize the infected lesion.

The acquired arteriovenous fistulas secondary to aneurysmal rupture of the aorta pose a difficult surgical problem. The dangers of rupture of a thin-walled aneurysm make any surgical procedure hazardous, and the difficulties of reconstruction are very great. However, it is probable that surgical procedures will be developed to the point to where at least some of the patients may be saved. Since the aneurysms of the aorta are practically always syphilitic in origin, there arises the problem of antisyphilitic therapy in such cases. Although we have had no serious complications in the cases where penicillin alone was used, it would appear desirable to give a preliminary course of iodide and bismuth therapy in order to avoid potentially serious Herxheimer reactions.

THE UNUSUAL PHYSICAL SIGNS

All extracardiac arteriovenous aneurysms present certain features in common—those findings dependent upon the existence of a shunt between a vessel of relatively high pressure to a vessel of low pressure. The flow of blood through this shunt results in the typical continuous murmur with systolic accentuation

heard with maximum intensity over the shunt and thus outside of the cardiac borders. The palpatory evidence of such a communication is the presence of a purring thrill, which likewise may be continuous, but only systolic if the diastolic phase of the murmur is not intense. In some cases the murmur may be heard only in systole. In others, it must be differentiated from a to-and-fro murmur due to coexisting valvular disease.

We have observed in these three cases an accentuation of both the systolic and diastolic phases of the continuous murmur at the height of deep inspiration and were able to record this intensification on the phonocardiograms. In fact, in the patient with pulmonary hemangioma, the diastolic phase of the murmur could be heard only on deep inspiration. The intensification of the murmur on inspiration is well accepted in cases of pulmonary hemangioma,[12,15] but it has not been emphasized in other arteriovenous communications within the thorax.

It is a well-accepted observation that most murmurs of organic, as well as functional, valvular disease are most intense on full expiration and become more distant on deep inspiration. This is attributed to the cushioning effect of expanded, air-filled alveoli, which decrease the transmission of the intracardiac sounds. One notable exception to this rule is the murmur of tricuspid valvular disease, both stenosis and insufficiency, as described by Rivero Carvallo[25] and Aceves and Carral.[27]

The explanation probably is the greater differential of expansion in the thin-walled venous systems of the thorax than in the arterial systems in response to the increased negative intrathoracic pressure of deep inspiration. Of course, this intensification of the murmur is partially counterbalanced by the increased air-filled tissue in inspiration, and in some cases this decreased transmission could overbalance the intensification. Nevertheless, this observation should be studied in other cases, as it may provide an additional clue to diagnosis.

SUMMARY

The historical background and delineation of the clinical features in the various types of extracardiac arteriovenous aneurysms within the thorax are described. To illustrate each type, there are presented detailed reports of three unusual cases:

1. Rupture of the aorta into the pulmonary artery: clinically diagnosed, verified by intracardiac catheterization, and made unusual by long survival.
2. Rupture of the aorta into the superior vena cava: clinically diagnosed, proved by oxygen content of venous blood at various sites, and confirmed at autopsy.
3. Pulmonary arteriovenous fistulas: the second reported case complicated by subacute bacterial endarteritis, which was eradicated by heavy penicillin therapy. Later, lobectomy and dissection of two smaller lesions in other lobes cured the condition.

Newer techniques of radiological examination, including planimetry and angiocardiography, determination of oxygen content of peripheral venous blood, and intracardiac catheterization, are now available in suitable cases to aid in the diagnosis. Intensification of the classical murmur on inspiration was noted in each of our three cases and needs further study as a possible diagnostic clue.

ADDENDUM

Recent reports on arteriovenous fistulas of the lungs included in the totals but not in the references are: Lindskog, G. E., Liebow, A., Kausel, H., and Janzen, A.: Ann Surg. **132**:591, 1950; Lawrence, E. A., and Rumel, W. R.: J. Thoracic Surg. **20**:142, 1950; Carswell, J., Jr.: J. Thoracic Surg. **19**:789, 1950. Each pointed out that the triad of cyanosis, polycythemia, and clubbing may not be present, but may develop in adolescence or adult life due to progressive increase in the size of the shunt.

The authors express their appreciation for the assistance of Dr. Sol Forman, the resident physician on the ward on which two of these patients were studied.

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THE USE OF A CARBOXYLIC CATION EXCHANGE RESIN IN THE THERAPY OF CONGESTIVE HEART FAILURE

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RESTRICTION of dietary sodium is recognized as a major keystone in the therapy of congestive heart failure, the nephrotic syndrome, and cirrhosis of the liver with ascites. However, the difficulties of maintaining a diet low in salt, particularly in the nonhospitalized patient, are great. A low-sodium diet is difficult to arrange and prepare and lacks taste and variety. Even with strict observance of the diet, many patients require frequent mercurial injections to lessen their symptoms. A possible way of circumventing these difficulties was suggested by Dock in 1946,[1] using the principle of ion exchange. Ion exchangers are insoluble substances, natural or synthetic, which have the property of removing one sort of ion from solution in exchange for another. Anion exchangers remove chloride, sulfate, and phosphate from solution and have found clinical use in the therapy of peptic ulcer.[2-6] Cation exchangers remove sodium, potassium, and calcium from solution. Dock showed, by feeding a cation exchange resin to rats, that sodium was removed from ingested food in the gastrointestinal tract and excreted with the feces. In 1949, Irwin and associates[7] published a careful balance study on the use of a sulfonated cation exchange resin in a human subject, and since then a number of reports have appeared in the literature[8-13] describing the feasibility of this approach to the problem of dietary sodium control. Dock and Frank[14] have recently given a complete summary of the subject.

Most cation exchangers in clinical use are synthetic resins which have been either sulfonated or carboxylated. Both types have a greater affinity for bivalent than for univalent ions. They differ mainly, as regards chemical action, in that the sulfonated resins maintain their exchange activity over a wide range of pH, whereas the carboxylic resins are most effective in removing cations in an alkaline medium. In the gastrointestinal tract below the duodenum, both resin forms are effective in binding the basic ions to the insoluble exchanger which takes them with it out of the body.

The first cation resins used in man exchanged free hydrogen ions for other cations with the result that acidosis was a frequent concomitant to resin therapy. Resins which exchanged ammonium ions for other cations also produced acidosis, in somewhat the same manner as the ingestion of large amounts of ammonium chloride. Acidosis was particularly prone to develop in patients with poor renal function where the compensatory mechanism of increased ammonia production

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was impaired. Negative potassium balance with development of hypokalemia was another danger incident to the use of both the hydrogen and the ammonium exchangers.

To combat these risks, resins have been devised which exchange ions other than hydrogen or ammonium, notably potassium, for the cations. Theoretically, a potassium exchanger should be useful because of its ability to prevent potassium depletion as well as to reduce the severity of acidosis by supplying a basic ion. Here, however, the risk of hyperpotassemia is great. Recently, mixtures of ammonium and potassium exchangers have been introduced for clinical use in an attempt to find a balanced combination of these resins which might reduce the dangers of acidosis and of potassium disturbance. Such a resin* has been used in this series of cases.

The aim of this study was to determine the practicability of using this cation exchange resin under conditions of private or clinic practice and to formulate a reasonable plan for following patients while on resin therapy. In all, seven patients were treated with this resin for periods of time ranging from six weeks to one year, predominantly on an outpatient basis.

MATERIALS AND METHODS

The resin used in these studies was a cross-linked polyacrylic carboxylic acid cation exchange resin, each 15 Gm. of which contained 3.3 Gm. of the potassium form and 11.7 Gm. of the ammonium form. It was supplied in packets of 15 Gm. each in the form of an insoluble, fine, white powder. Patients were advised to mix the resin well in either water or salt-free tomato juice. Resin dosage varied between 30 and 60 Gm. a day given in divided doses with meals.

Six patients with chronic congestive heart failure were selected for treatment. All of them had responded poorly to the usual therapy with digitalis, salt restriction, and mercurial diuretics. In addition, a patient in the nephrotic phase of chronic glomerulonephritis received resin therapy. The subjects, while outpatients, were examined about once a week. They were instructed to make no changes in their usual food consumption while taking resin. It was estimated, in most cases, that the diet contained between 3 and 5 Gm. of sodium chloride daily.

At each weekly visit, physical examination and weight were recorded. Mercurial diuretics were given as indicated by the clinical state. Determinations were made weekly of serum sodium, potassium, calcium, chlorides, and carbon dioxide combining power. In those patients who exhibited neither clinical nor chemical evidences of toxicity, visits were spaced at two- and occasionally at three-week intervals.

Sodium and potassium determinations were performed with an internal flame photometer.[15] Calcium was determined by the method of Sobel and Sobel,[16] chloride according to Schales and Schales,[17] and carbon dioxide combining power by the method of Van Slyke and Neill.[18]

*Supplied by Smith, Kline & French Laboratories, Philadelphia, Pa., and now marketed under the trade name of Resodec.

CASE REPORTS

CASE 1.—Y. K., a 71-year-old housewife, was known to have had arterial hypertension for over ten years and symptoms of congestive heart failure for two years. Although never able to maintain a low-salt diet, she had taken digitoxin daily and an injection of Mercuhydrin weekly for many months. Despite these measures, physical examination at the start of the investigative period revealed distended neck veins, hepatosplenomegaly, and edema of the sacrum and legs. The major complaint was exertional dyspnea.

The patient was started on 45 Gm. of the cation exchange resin daily, keeping the diet, estimated at 4 Gm. of sodium chloride daily, unchanged (Fig. 1). She continued this dosage for an uninterrupted period of thirteen weeks, during which time she required no Mercuhydrin. The weight fell slightly from 145 pounds to fluctuate beween 140 and 142 pounds. The neck vein distention became less marked, although the other objective evidences of congestive failure persisted. Subjectively, the patient noted decided relief of exertional dyspnea and orthopnea.

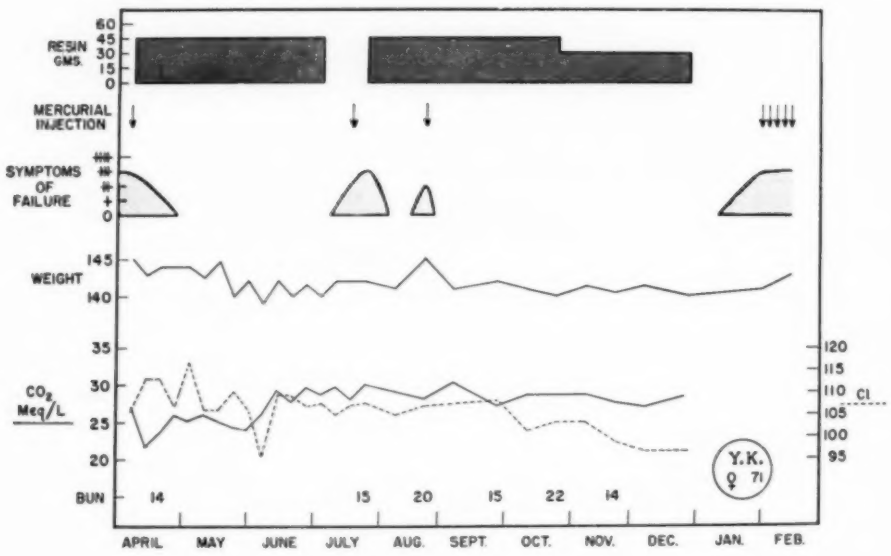

Fig. 1 (Case 1).—This patient in chronic cardiac failure took resin for thirty-five weeks. Although there was only a moderate fall in weight, she had decided relief of dyspnea and orthopnea. There were no untoward reactions to the resin.

The resin was discontinued, and within two weeks the symptoms returned. One mercurial injection gave little relief. She was restarted on the resin in the same dosage with prompt subsidence of dyspnea and orthopnea. Thereafter, she took the resin for another uninterrupted period of twenty-two weeks, requiring only one injection of Mercuhydrin which was given because of a 4 pound weight gain following dietary indiscretions. The dose of resin was reduced to 30 Gm. a day during the last nine weeks of the study period with no increase in weight or return of symptoms. After final discontinuance of the drug, the patient was followed for an additional seven weeks during which time there was a gradual return of decompensation so that when last examined, she was being given Mercuhydrin injections twice weekly.

In this patient, who was treated on an ambulatory basis, the resin was a satisfactory substitute for mercurial diuretics. After thirty-five weeks of resin therapy, there were no clinical or chemical evidences of toxicity. Significant changes did not occur in the blood levels of carbon dioxide combining power,

chloride, sodium, calcium, or urea nitrogen. A transient fall in the serum potassium level to 3.0 meq. per liter early in the course of therapy was not associated with clinical symptoms.

CASE 2.—I. R., a 50-year-old clothing salesman, had had hypertension for many years and severe congestive heart failure for one and one-half years, during which time he worked only sporadically. Despite moderate dietary restriction of salt, digitoxin, and injections of Mercuhydrin twice a week, he complained of incapacitating exertional dyspnea, orthopnea, nocturnal paroxysmal dyspnea, and occasional ankle edema. Physical examination disclosed cardiac enlargement, auricular fibrillation, and hepatosplenomegaly without peripheral edema.

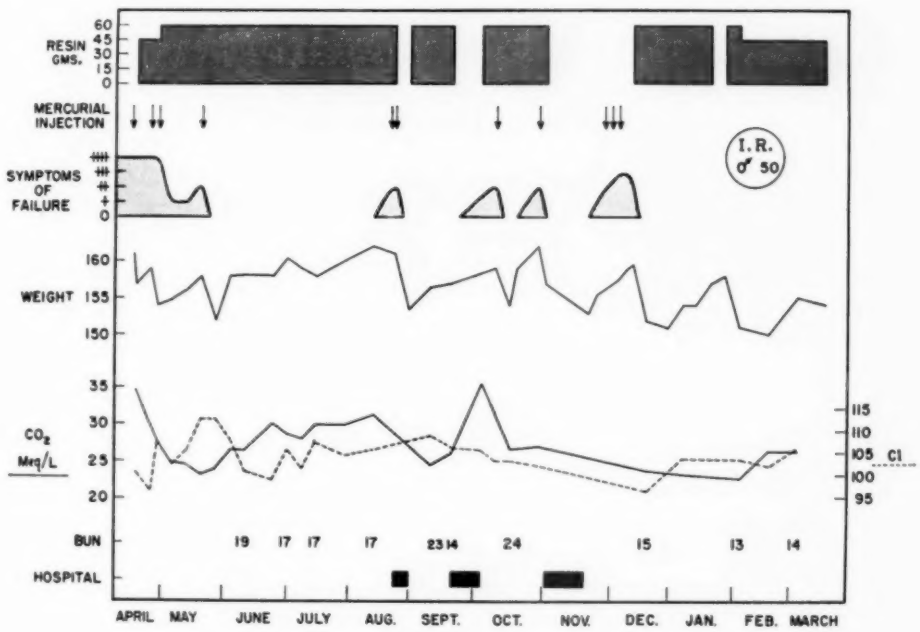

Fig. 2 (Case 2).—**This patient has had marked symptomatic relief on resin therapy. No clinical or chemical evidences of toxicity have developed during the year he has taken resin.**

The patient was started on 45 Gm. of the cation exchange resin daily and instructed to maintain the usual diet, estimated to contain 3 Gm. of sodium chloride (Fig. 2). Although there was a moderate drop in weight, the patient's symptoms continued necessitating injections of mercurials in addition to the resin. The dose of the drug was then raised to 60 Gm. a day with almost immediate relief of the symptoms. Shortly thereafter, the patient was able to return to work. He remained asymptomatic for the next three weeks, but then, coincident with dietary indiscretions, there was a return of dyspnea and orthopnea requiring Mercuhydrin. For the next three months he remained free of symptoms on resin therapy.

In August, 1950, he was admitted to the hospital for the first of three occasions over the next five months, during each of which resin therapy was temporarily discontinued. Two of these admissions were for episodes of flank pain associated with microscopic hematuria. A third episode of flank pain was treated at home. Genitourinary work-up, including intravenous and retrograde pyelography, did not reveal evidence of calculi, and it was thought that these symptoms were caused by emboli arising from the fibrillating heart. The third admission was for a cerebrovascular accident, again probably an embolus, which cleared without sequelae. During this last admission and the period immediately following hospitalization, an attempt was made to wean

him from the resin. Despite mercurials, however, the weight rose steadily, and he was increasingly more dyspneic and orthopneic. The resin was restarted, and again he became symptom free.

This patient has taken resin for more than one year thus far, most of the time as an outpatient. There have been no untoward effects which seem attributable to the use of this cation exchange resin, except for transient, asymptomatic drops in serum calcium (to 8.3 mg. per cent) and potassium (to 2.8 meq. per liter). For the first time in a year and one-half he was able to hold a job until the multiple embolizations reduced his working efficiency. With moderate dietary salt restriction, the cation exchange resin more than replaced Mercuhydrin in this patient. At the present time (Sept. 6, 1951) he is still on resin therapy.

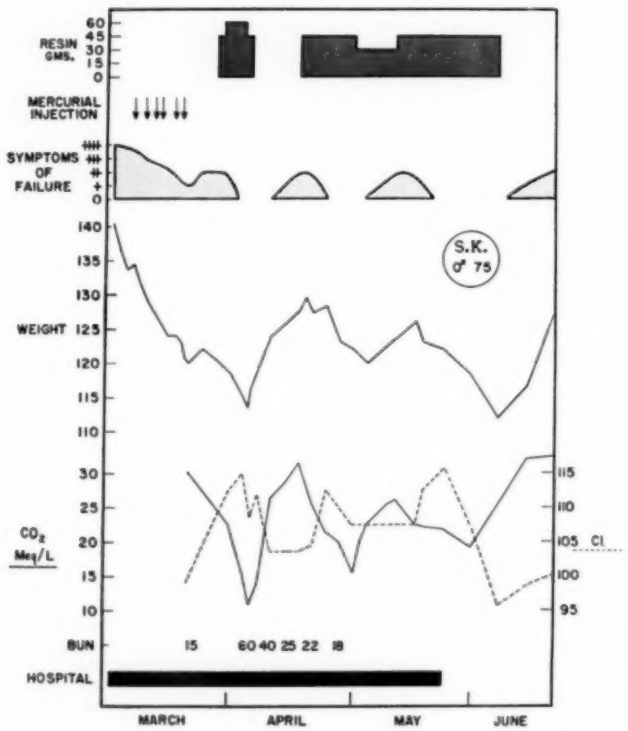

Fig. 3 (Case 3).—The dosage of resin could not be adjusted in this patient so that the symptoms of failure could be controlled without precipitating acidosis. He had a severe episode of hyperchloremic acidosis early in April, 1950.

CASE 3.—S. K., a 75-year-old man, had had known arteriosclerotic heart disease with symptoms of congestive heart failure for the past six years. The history included an episode of myocardial infarction nine years prior to this study. Fair cardiac compensation was maintained with digoxin, salt restriction, and mercurial diuretics given one to two times a week. The numerous episodes of cardiac decompensation during the six years were usually related to lack of adequate sodium restriction in the diet. Although the blood urea nitrogen was only 15 mg. per cent, a phenolsulfonphthalein excretion of 30 per cent in two hours and inability to concentrate urine above a specific gravity of 1.012 indicated impairment of renal function. At the start of the investigative period, physical examination revealed an enlarged heart, auricular fibrillation, distended neck veins, right hydrothorax, ascites, hepatomegaly, and ankle edema.

He was placed on a 1.5 Gm. sodium chloride diet, maintenance doses of digoxin, and Mercuhydrin injections three times a week, with a resultant 20 pound loss in weight (Fig. 3). Evidences of chronic congestive heart failure persisted despite this regimen. Mercurials were then withheld for a ten-day period during which time the weight remained at about 120 pounds. Cation exchange resin was started in a dosage of 60 Gm. a day. By the end of the first week of resin therapy, there had been a further loss of 6 pounds in weight, but the patient exhibited increasing weakness, somnolence, and oliguria. The blood urea nitrogen rose to 60 mg. per cent, and he developed a hyperchloremic acidosis with a fall in carbon dioxide to 11.0 meq. per liter and a rise of serum chlorides to 115.0 meq. per liter. The resin was discontinued, and on supplementary salt, fluids, and alkali there was rapid improvement. During the acute episode, electrocardiographic and clinical evidences of digitalis toxicity developed coincident with a fall in serum potassium to 3.2 meq. per liter. Serum sodium remained within normal limits.

Resin was restarted in doses of 45 Gm. a day with a subsequent slow, but steady, fall in serum carbon dioxide to 15.8 meq. per liter. There were no symptoms at that time, but it was thought best to reduce the dose of resin to 30 Gm. daily. This dose proved too small, as there was an increase in symptoms of heart failure and a 3½ pound weight gain over the next week. The dosage of resin was again raised to 45 Gm. a day. This time there was only a moderate fall in the carbon dioxide combining power, and, since the patient remained asymptomatic, he was discharged from the hospital. At this time, he still had right pleural effusion, hepatomegaly, and ankle edema, but was neither dyspneic nor orthopneic.

Resin was continued after discharge in a dosage of 45 Gm. a day. Two weeks later the weight had fallen sharply to 112 pounds, and he complained of marked weakness and anorexia. Extremely hot weather at that time may have contributed to this result. Because of these symptoms, the resin was discontinued.

During the next two weeks there was a gain of 15 pounds in weight, associated with increased evidences of congestive heart failure. On the afternoon of June 21, 1950, shortly after his last visit to the clinic and fourteen days after his last dose of the resin, the patient died during sleep. Permission for autopsy could not be obtained, but it was felt that death was not related to resin therapy.

Although the resin was tried in varying amounts for two and one-half months, we were unable to adjust dosage so that cardiac decompensation could be controlled without precipitating acidosis in this patient. The rapid shifts in serum carbon dioxide illustrate the necessity for careful chemical control in these patients. In addition, the fall in serum potassium associated with evidence of digitalis toxicity is to be noted.

CASE 4.—I. K., a 65-year-old man, had had diabetes mellitus for sixteen years and was fairly well controlled on 15 to 20 units of protamine zinc insulin daily. He had many of the complications of diabetes including blindness following bilateral hemorrhagic glaucoma, hypertension, a cerebrovascular accident, and a myocardial infarction. Renal function was moderately reduced with concentration of urine to 1.015, occasional albuminuria, blood urea nitrogen of 15 mg. per cent, phenolsulfonphthalein excretion of 50 per cent in two hours, and a urea clearance of 90 per cent of normal. Since 1947, he had had symptoms of congestive heart failure. Despite dietary salt restriction, digitoxin, and semiweekly Mercuhydrin injections, there were frequent breaks in compensation during these three years. Physical examination at the start of the study period, with the patient hospitalized, disclosed scattered râles at the right posterior lung base, an enlarged heart, and hepatomegaly. No peripheral edema was present.

During a control period the weight was reduced by 9½ pounds with mercurials. The patient was then started on 45 Gm. of the cation exchange resin daily (Fig. 4). The following week the dose was raised to 60 Gm. a day. For the first three weeks, he not only did not require mercurials but lost 5 pounds in weight. He was discharged from the hospital to continue the same regimen at home. This included a diet which was estimated to contain about 4 Gm. of salt daily. One

week later the carbon dioxide combining power had fallen sharply to 17.5 mEq. per liter, but the patient had no symptoms until two weeks later when extremely hot weather set in. At this time the patient had to be readmitted because of marked weakness. Blood chemical findings revealed a serum sodium of 131.4 meq. per liter and a rise in blood urea nitrogen to 38 mg. per cent. Resin was temporarily discontinued, and the patient was given additional salt orally with prompt subsidence of symptoms and return of the blood chemistry to normal. He was discharged from the hospital after five days and restarted on 45 Gm. of resin daily. Readmission was necessitated ten days later for treatment of gangrene of the right fifth toe, and the patient remained in the hospital for the remainder of the study period.

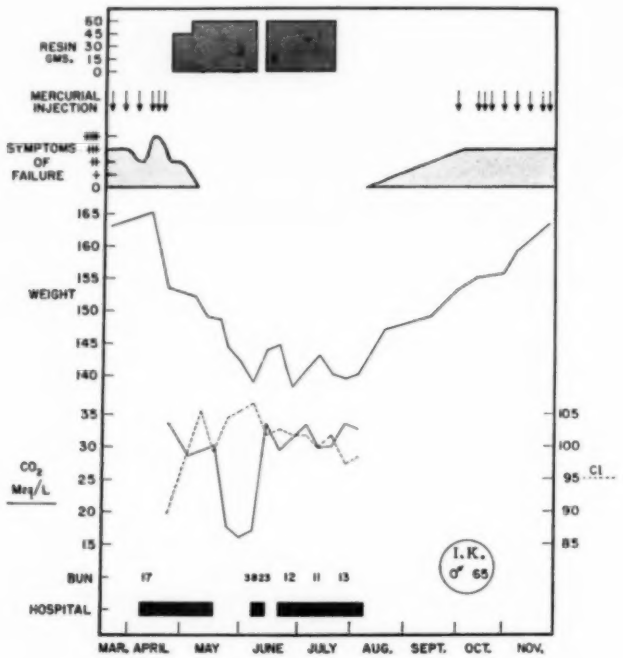

Fig. 4 (Case 4).—This diabetic patient had definite relief of the symptoms of congestive heart failure while on resin. The episode of acidosis was complicated by salt depletion during unusually hot weather.

There were no subsequent complications while the patient was on resin therapy, and the drug was discontinued after a period of three months. The weight stabilized at about 140 pounds, and the patient was free of the symptoms of congestive heart failure without supplementary mercurials. He was followed for an additional four months after final discontinuance of resin and showed a gradual return of the weight to pretreatment levels despite twice weekly Mercuhydrin injections.

It seemed that the resin was an adequate substitute for mercurials in this patient. The episode of acidosis was undoubtedly produced by resin therapy, but it seems likely that the symptoms of salt depletion were precipitated by unusually hot weather. Serum levels of potassium and calcium did not change significantly while the patient was receiving resin.

CASE 5.—J. L., a 50-year-old housewife, had had many attacks of acute rheumatic fever since the age of 6 years and for the past eleven years had had frequent hospital admissions for chronic

cardiac failure, responding only partially to digitalis, mercurials, and salt restriction. In addition, she had episodes of abdominal pain ascribed to chronic cholecystitis and cholelithiasis.

At the time of her most recent hospitalization in April, 1950, she was in frank cardiac decompensation with enlarged heart, auricular fibrillation, hepatomegaly, and peripheral edema. After an initial 7 pound loss, the weight stabilized at about 173 pounds despite almost daily mercurials as well as full digitalization and salt restriction.

Resin was started but had to be discontinued because of nausea and vomiting. Again mercurials failed to effect a diuretic response, and accordingly the resin was restarted in doses of 45 Gm. per day, this time without gastric distress. There was a prompt and steady improvement in the cardiac status on resin therapy, and, over the next month, the patient lost 7 more pounds although never reaching dry weight. Three mercurial injections were then given with a further drop in weight of 5 pounds (Fig. 5).

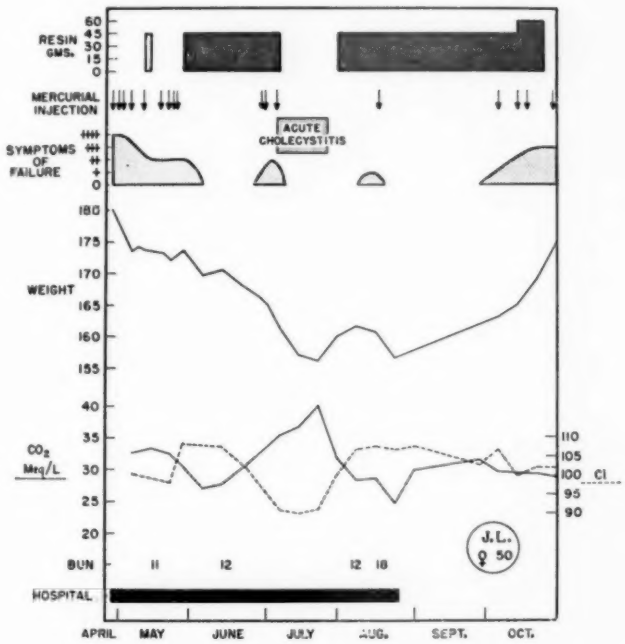

Fig. 5 (Case 5).—This rheumatic patient was relieved of dyspnea and orthopnea during therapy with the resin. The episode of alkalosis occurred during an attack of cholecystitis. The patient appeared to become resistant to both mercurials and resin at the end of the study period.

At this point the patient developed an attack of acute cholecystitis. She became nauseated and vomited all feedings, and the resin had to be stopped for a period of one month. While ill with the gall bladder episode, she developed alkalosis with hypopotassemia and hyponatremia.

The resin was restarted in August, 1950, and continued in uninterrupted dosage for the next three months, the last two months on an outpatient basis. Toward the end of the investigative period, the patient became resistant to resin as well as to Mercuhydrin and gained weight rapidly.

During the six-month period in which this patient was followed, she seemed to tolerate resin well and showed no toxic effects attributable to the medication except for the transient episode of gastric distress. The number of mercurial injections required was sharply diminished although, toward the end of the resin period, she gained weight despite resin and mercurials.

CASE 6.—N. K., a 46-year-old housewife, had had well-documented rheumatic heart disease and the symptoms of chronic heart failure for the past seven years. She maintained a fair low-sodium diet but took digitalis and mercurial diuretics only sporadically. Physical examination disclosed distended neck veins, hepatomegaly, and peripheral edema.

The patient was started on 45 Gm. of the cation exchange resin daily. Because of weight gain and continued symptoms, the dose was raised to 60 Gm. a day. On this regimen, while the patient was consuming an estimated 3 Gm. of sodium chloride daily, the weight stabilized, and she was comfortable. The peripheral edema persisted.

The study period had to be terminated because the patient left this city. When resin was discontinued, the weight rose sharply, and the symptoms returned; she required mercurial injections at weekly intervals.

Although the patient received this resin for only six weeks, it appeared that it was a satisfactory substitute for mercurials. There were no significant changes in the blood chemical values nor were there clinical evidences of toxicity to the resin.

CASE 7.—I. E., a 49-year-old fruit vender, had the onset of periorbital and ankle edema in March, 1949. These symptoms persisted until the first hospital admission in September, 1949, where examination disclosed albuminuria, hypoalbuminemia, and hypercholesterolemia. A diagnosis of the nephrotic stage of chronic glomerulonephritis was made.

The edema persisted virtually unchanged despite dietary sodium restriction. He did not receive mercurial injections. In March, 1950 (one year after the onset of edema), the patient was started on the cation exchange resin in a dosage of 60 Gm. per day. The weight in the months prior to institution of resin therapy had fluctuated spontaneously between 150 and 160 pounds. At the beginning of the therapeutic program he weighed 158 pounds and was placed on a diet that contained 4 Gm. of salt daily.

The patient took this resin for an uninterrupted period of twelve weeks, during which time there were no essential changes in weight nor in the clinical state of edema. The daily salt intake was reduced to from 1.5 to 2.0 Gm. a day, again without effect.

The patient tolerated the resin well until a few days before cessation of therapy when he complained of nausea and weakness. A mild episode of hyperchloremic acidosis, with a fall in carbon dioxide to 18.8 meq. per liter and a rise in chloride to 113.9 meq. per liter, may have contributed to this. The serum sodium remained unchanged during the twelve weeks of resin therapy, but there was a moderate fall in serum potassium to a low of 3.4 meq. per liter, unassociated with clinical hypokalemia. The serum calcium was 7.6 mg. per cent at the onset of therapy and rose to 8.8 mg. per cent during the period of resin administration. The serum albumin ranged between 1.5 and 2.0 Gm. per cent at that time.

Resin therapy did not appear to initiate a diuresis in this patient with the nephrotic syndrome.

DISCUSSION

Six patients with chronic congestive heart failure were treated with this carboxylic cation exchange resin which contained a mixture of the ammonium and potassium forms. Five appeared to be benefited by therapy. In only two of our patients did this resin appear to be ineffectual. Case 3 was an elderly man with arteriosclerotic heart disease and impairment of renal function. We were unable to find the dosage of resin which would control the symptoms of failure without precipitating acidosis. The other patient (Case 7), a middle-aged man in the nephrotic phase of chronic glomerulonephritis, had no diuresis while on resin therapy.

Despite these two poor results, the advantages of cation exchange resin therapy are clear. The cooperative patient is allowed a freer and more appetizing diet. The patient who knowingly or unknowingly does not follow his diet can be more easily and more efficiently controlled. The necessity for mercurial injections, with their attendant inconvenience and pain, may be sharply reduced. In some patients (Cases 1, 2, 4, 5, and 6) the resin seemed superior to Mercuhydrin in controlling the weight and the symptoms of cardiac failure. Finally, in those patients who tolerate the resin well, the frequency of clinic visits may be greatly reduced.

As promising as this sounds, the possible toxic effects of resin therapy should be emphasized. The physician must be on the alert for clinical or chemical evidences of intolerance to the drug. Particular care must be shown in watching for the following:

1. Acidosis.—The resin used in this study was devised in an attempt to counteract the tendency to acidosis inherent in therapy with the ammonium and hydrogen forms. Its partial success is evident from these studies. Four of our patients (Cases 1, 2, 5, and 6) showed no significant changes in the carbon dioxide combining power attributable to resin therapy. Two patients developed compensated acidosis (Cases 4 and 7). The other patient (Case 3) developed a clinical picture of apathy, weakness, stupor, and anorexia with a fall in carbon dioxide to 11 meq. per liter, which was probably a severe uncompensated acidosis. It should be emphasized that this patient had some impairment of kidney function and that resin dosage may have been excessive. He responded quickly to therapy with salt, alkali, and fluids.

2. Sodium and Potassium Depletion.—One patient (Case 4) developed a low serum sodium while on resin therapy. Extremely hot weather appeared to play a role in the development of this episode of salt depletion.

Despite the fact that this resin contained 20 meq. of potassium per 15 Gm. of resin, there was a moderate fall in serum potassium at some time during the course of therapy in four patients (Cases 1, 2, 3, and 7). Only in Case 3, however, was this of clinical significance. Hypokalemia in this patient was associated with evidences of digitalis toxicity. The possible antagonistic effects and relationships of potassium and digitalis have recently been re-emphasized.[19]

3. Calcium Depletion.—The in vitro affinity of cation exchange resins for bivalent ions, calcium in particular, has been pointed out[7] and would appear to make hypocalcemic tetany a distinct risk of resin treatment. In clinical use, however, hypocalcemia rarely develops. The low concentration of calcium in intestinal fluids[7] tends to mitigate serious loss of this cation, while the development of acidosis would tend to prevent clinical tetany even if hypocalcemia did develop. Dock and Frank[14] mentioned two cases of tetany following the use of resins. Although there was a transient fall in serum calcium levels in two of our patients, none manifested overt tetany. We did not supplement the diet with additional calcium. Case 7, a patient with the nephrotic syndrome, had a low serum calcium (associated with hypoproteinemia) before institution of resin, and the level rose slightly during therapy.

4. Gastrointestinal Irritation.—Resin was administered to one other patient in addition to those already detailed. He was a 57-year-old man in congestive heart failure due to syphilitic heart disease. He took resin for only a few days, discontinuing the medication because of marked nausea and vomiting. Except for this case and a transient episode of nausea and vomiting in Case 5, there were no other instances of nausea, although some of our patients took resin for almost a year. Most of the patients complained of the gritty taste of the powders but were more than willing to continue the medication when the clinical benefits following its use became apparent.

Clinical evidences of vitamin deficiency developing in patients on resin therapy were not observed. Nor did we observe any apparent effect on arterial pressure in the dosages we employed. Blood counts, performed at the start and finish of resin administration, were unchanged.

In our experience the carbon dioxide combining power seemed to be the first determination to change with the development of untoward reactions. Toxicity did not take place in our patients until the carbon dioxide had fallen below 20 meq. per liter. The onset of toxic symptoms or a fall in carbon dioxide below 20 meq. per liter seems an indication for either reducing the dose of resin or discontinuing the medication altogether.

Our experience with this cation exchange resin is too small to permit generalizations. However, it appears that this resin can be given to selected ambulatory patients with congestive heart failure when facilities are available for following them both clinically and with chemical determinations of their sera. Special care seems indicated in people who eat poorly while taking resin because of the possibility of salt depletion. The patient must be carefully watched during unusually hot weather where excessive loss of sodium through sweating again makes hyponatremia a distinct risk. A sharp, sudden drop in weight or onset of weakness, apathy, and anorexia may presage the onset of toxicity. Extreme caution must be exercised when the resin is given to patients with impairment of renal function.

SUMMARY

1. A carboxylic acid cation exchange resin, containing a mixture of the ammonium and potassium forms, was administered to six cardiac patients and one patient with the nephrotic syndrome, predominantly on an outpatient basis, for periods ranging from six weeks to one year. One other cardiac patient was unable to tolerate the drug because of gastric distress.

2. Five of the six cardiac patients were benefited by therapy to the extent that there was a marked reduction in the number of mercurial injections necessary to keep them symptom free. The other cardiac patient, who had impairment of renal function, had a toxic reaction in the form of an uncompensated acidosis. He also developed hypokalemia with evidences of digitalis intoxication. One patient had an episode of salt depletion during unusually hot weather. A diuresis was not induced in the nephrotic patient by therapy with this resin.

3. The use of this resin appears to be practical for the treatment of ambulatory patients with cardiac failure who can be followed closely. A carbon dioxide combining power above 20 meq. per liter appears to be a safe level.

4. The resin should be used with extreme caution in patients with inadequate renal function.

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A METHOD FOR THE OBJECTIVE EVALUATION OF PHYSICAL AND DRUG THERAPY IN THE REHABILITATION OF THE HEMIPLEGIC PATIENT

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THE use of physical therapeutic and rehabilitation measures in the treatment of hemiplegia seems well established,[1-3] but objective measurements of results have been in qualitative rather than quantitative terms. As Dinken[4] has indicated, such objective measurements should include "determination of muscle strength, range of joint motion and functional testing of the factors inherent in daily living."

The value of a new therapeutic approach in the management of hemiplegia can only be assessed by its ability to shorten the time-course of rehabilitation, such effects, if any, being rigidly compared with those obtained in adequate controls. The time-course of rehabilitation may be defined as the shortest interval in days between the onset of treatment and the greatest retained achievement in range of joint motion, muscle strength, and performance of tasks of daily living.

This report describes an objective technique, established to study the effect of physical therapeutic and rehabilitation techniques on the time-course of rehabilitation in the subject with hemiplegia as the result of a cerebrovascular accident. In addition, it can be used to screen the effects of drugs on this clinical entity. There is great need for such a method at the present time.

METHODS

Selection of Patients.—Case selection is made to limit patients to those with cerebral thrombosis or embolism. Patients with cerebrovascular accidents due to cerebral hemorrhage, at least during acute phases, are excluded from study because of the possibility of further cerebral bleeding. Also excluded are patients in whom it is believed that the pathologic process would progress more rapidly than rehabilitation, namely (1) malignant hypertension, (2) severe encephalomalacia, and (3) intractable cardiac insufficiency or failure.

All patients receive a complete diagnostic survey including roentgen examination of the heart and lungs, electrocardiogram, urinalysis, blood counts, and blood chemistries. Lumbar puncture is performed when indicated. Before the start of treatment all patients are evaluated, with the use of the methods de-

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tailed, by physical therapy and occupational therapy personnel of the Rehabilitation Service with regard to the following modalities: (1) muscle strength (Charts 1*A* and 1*B*), (2) passive range of joint motion (Chart 2), and (3) ability to perform the activities of daily living (Chart 3). The results are recorded by a quantitative method, modified from Dinken,[4] which permits objective comparison of serial examinations.

Patients for a specific study group are selected by the chance drawing of slips marked "drug" and "placebo" from a hat. It is deemed desirable to attempt to match the patients with respect to age, sex, and etiology, duration, and severity of hemiplegia.

LEFT						RIGHT
					Examiner's Initials	
					Date	
SHOULDER					Flexors	SHOULDER
					Extensors	
					Abductors	
					Horizontal Abductor	
					Horizontal Adductor	
					External rotators	
					Internal rotators	
ELBOW					Flexors	ELBOW
					Extensors	
FOREARM					Supinators	FOREARM
					Pronators	
WRIST					Flexor-radial deviation	WRIST
					Flexor-ulnar deviation	
					Extensors-radial deviation	
					Extensor-ulnar deviation	
FINGERS					1 Flexor profundus digitorum 1	FINGERS
					2 " " " 2	
					3 " " " 3	
					4 " " " 4	
					1 Flexor sublimis digitorum 1	
					2 " " " 2	
					3 " " " 3	
					4 " " " 4	
					1 Finger Extensors 1	
					2 " " 2	
					3 " " 3	
					4 " " 4	
					1 Lumbricales 1	
					2 " 2	
					3 " 3	
					4 " 4	
					Dorsal interossei	
					Palmer interossei	
THUMB					Opponens pollicis	THUMB
					Adductor pollicis	
					Abductor pollicis longus	
					Abductor pollicis brevis	
					Thumb extensors	
					Flexor pollicis longus	
					Flexor pollicis brevis	
					CONTRACTIONS AND DEFORMITIES	
					SHOULDER	
					ELBOW	
					FOREARM	
					WRIST	
					FINGERS	
					THUMB	

DATE..... THERAPIST.....

Chart 1*A*.—Muscle strength.

Administration of Medication.—The "double-blind" method of medication is employed. In this system oral medications are prepared so that the drug and placebo tablets resemble each other in size, shape, taste, and color. In addition, intravenous medications are matched as to color and vial size. Neither the examining physicians nor the patients are aware of whether drug or placebo is being administered during the therapeutic course. It is only at the end of the study that the code is broken.

Method for Measuring and Recording the Modalities Tested.—

1. Muscle strength: This is tested in a systematic manner[5] by physiotherapy technicians using the Brunnstrom[6] modification of the Lovett[7,8] method

NAME WARD CLINIC

LEFT BELLEVUE HOSPITAL RIGHT

					Examiner's Initials							
					Date							
HIP					Flexors							HIP
					Extensors							
					Abductor							
					Adductors							
					External Rotators							
					Internal Rotators							
					Sartorius							
					Tensor fasciae latae							
KNEE					Flexor-outer hamstring							KNEE
					Flexors-inner hamstrings							
					Extensors							
ANKLE					Plantar-flexors-Gastroc. & Soleus							ANKLE
					Plantar-flexor-Soleus							
FOOT					Invertor-Anterior tibial							FOOT
					Invertor-Posterior tibial							
					Evertor-Peroneus brevis & longus							
					Evertor-Peroneus tertius							
TOES					1 Extensor longus digitorum 1							TOES
					2 " " " 2							
					3 " " " 3							
					4 " " " 4							
					1 Extensor brevis digitorum 1							
					2 " " " 2							
					3 " " " 3							
					4 " " " 4							
					1 Flexor longus digitorum 1							
					2 " " " 2							
					3 " " " 3							
					4 " " " 4							
					1 Flexor brevis digitorum 1							
					2 " " " 2							
					3 " " " 3							
					4 " " " 4							
					1 Lumbricales 1							
					2 " 2							
					3 " 3							
					4 " 4							
HALLUX					Extensor proprius hallucis							HALLUX
					Flexor longus hallucis							
					Flexor brevis hallucis							
					CONTRACTIONS AND DEFORMITIES							
					NECK							
					BACK							
					HIP							
					ANKLE							
					FOOT							

Chart 1*B*.—Muscle strength.

Name: Ward: Date:
Diagnosis: Disability: Joint:

Range of Motion Chart

Range is measured with cauda as zero, cranium as 180°, in rotating motions from midsagittal plane as zero to lateral plane as 180°. A = active, P = passive range of motion. Passive motion may be forced up to the threshold of pain.
The scale is divided in units of 15°. Range of motion is recorded by filling in the blocks in black. ◤ means that only the first named, ◢ that only the second named motion is possible. Progress is recorded by filling in the blocks in red, retrogression by marking X across the block, and by noting the dates under Comments.

Joint	Motion and Range		Left	Right
			15 30 45 60 75 90 105 120 135 150 165	15 30 45 60 75 90 105 120 135 150 165
Shoulder	Flexion-Extension	A		
	0-180	P		
	Abduct-Adduction	A		
	0-180	P		
	Int-Ext Rotation	A		
	0-180	P		
Elbow	Flexion-Extension	A		
	0-150	P		
	Pronation-Supin	A		
	0-180	P		
Wrist	Dorsal-Palmar Fl	A		
	15-165	P		
	Radial-Ulnar Fl	A		
	60-150	P		
Hip	Flexion-Extension	A		
	0-120	P		
	Abduct-Adduction	A		
	0-45	P		
	Int-Ext Rotation	A		
	45-135	P		
Knee	Flexion-Extension	A		
	0-120	P		
Ankle	Dorsal-Plantar Fl	A		
	45-105	P		
	Invers-Eversion	A		
	60-120	P		
Toes	Flexion-Extension	A		
	60-165	P		
			15 30 45 60 75 90 105 120 135 150 165	15 30 45 60 75 90 105 120 135 150 165

Hand	Motion		Carp-Metac	Metacarpal Phalangeal	Proximal Phalangeal	Distal Phalangeal
Left			15 30 45	15 30 45 60 75 90	15 30 45 60 75 90 105 120	15 30 45 60 75
Thumb	Opposition and	A				
	Flexion-Extension	P				
2 Finger	Flexion and	A				
	Extension	P				
3 Finger	Flexion and	A				
	Extension	P				
4 Finger	Flexion and	A				
	Extension	P				
5 Finger	Flexion and	A				
	Extension	P				
Right				45	45 90	45
Thumb	Opposition and	A				
	Flexion-Extension	P				
2 Finger	Flexion and	A				
	Extension	P				
3 Finger	Flexion and	A				
	Extension	P				
4 Finger	Flexion and	A				
	Extension	P				
5 Finger	Flexion and	A				
	Extension	P				
			15 30 45	15 30 45 60 75 90	15 30 45 60 75 90 105 120	15 30 45 60 75

Chart 2.—Range of joint motion.

of manual muscle testing. By observing the ability of the muscle to contract against gradually increasing loads in the form of surface friction, gravity, and applied resistance, it is possible to record thirteen gradations of muscle strength in each of the muscle groups tested. These range from no muscular activity to normal muscle strength (Table I).

NAME DATE ADMITTED CASE NO. WARD

DIAGNOSIS AGE

ACTIVITIES INHERENT IN DAILY LIVING

	NON WALKING ACTIVITIES	GRADE	DATE
A	1. Roll to right, left		
	2. Sit erect in bed		
B	1. Comb or brush hair		
	2. Brush teeth		
	3. Shave or apply make-up		
	4. Wash extremities		
	5. Manipulate bed pan		
C	1. Cut meat		
	2. Butter bread		
	3. Eat with fork		
	4. Drink from glass		
	5. Stir coffee		
D	1. Dress		
	2. Tie shoestrings		
	3. Tie tie		
	4. Undress		
	5. Don braces		
	6. Remove braces		
E	1. Write name and address		
	2. Fold letter, seal envelope		
	3. Open envelope, remove letter		
	4. Open and close safety pin		
	5. Use dial telephone		
	6. Turn pages of book		
	7. Wind wrist watch		
	8. Strike match		
F	1. Bed to wheelchair		
	2. Wheelchair to bed		
	3. Raise, lower foot rests		
	4. Propel wheelchair		
	5. Open and close door		
	6. Wheelchair to chair		
	7. Chair to wheelchair		
	8. Wheelchair to toilet		
	9. Toilet to wheelchair		
	10. Wheelchair to bathtub		
	11. Bathtub to wheelchair		
	12. Floor to wheelchair		
G	1. Bed to erect position		
	2. Erect position to bed		
	3. Wheelchair to erect position		
	4. Erect position to wheelchair		
	5. Chair to erect position		
	6. Erect position to chair		
	7. Erect position to toilet		
	8. Toilet to erect position		
	9. Down to floor		
	10. Up on floor		

	WALKING ACTIVITIES	GRADE	DATE
H	1. Walk forward 30 feet		
	2. Walk backward 10 feet		
	3. Walk sideward 10 feet		
	4. Open and close door		
I	1. Open and close cylinder lock		
	2. Open and close ice box door		
	3. Open and close drawers		
	4. Open and close padlock with key		
	5. Open and close door hook		
	6. Open and close window		
	7. Pull window shade		
	8. Work light switches		
	9. Push door bell		
	10. Work pull chain light		
	11. Open and close cabinet lock		
	12. Turn faucet		
	13. Open and close medicine chest		
	14. Open and close bottle		
J	1. Up 15 degree ramp 3 feet		
	2. Down 15 degree ramp 3 feet		
	3. Flight of stairs (1) handrail		
	4. Flight of stairs no handrail		
	5. Up curb		
	6. Down curb		
K	1. Cross standard street on green light-40 seconds		
	2. Get in, out of bus, use turnstile-20 seconds		
	3. Erect position to car		
	4. Car to erect position		
	5. Pick up object from floor		
	6. Carry cafeteria tray with dishes		
	TOTAL NON WALKING (48)		
	TOTAL WALKING (30)		
	TOTAL ALL ACTIVITIES (78)		
	THERAPIST		

Chart 3.—Activities inherent in daily living.

To enhance the objectivity of the test, it is arranged for the same therapist to perform all the tests on a given patient throughout the course of the study. This minimizes the variations that may arise from individual differences in judging strength on the part of the therapists. However, it should be noted that the various gradations of strength are so defined that, with any group of therapists testing the same muscle group, variations of more than one gradation would be unusual and of more than two gradations rare.

TABLE I. NOMENCLATURE, CRITERIA, AND NUMERICAL SCORING FOR TESTING MUSCLE STRENGTH

NOMENCLATURE		CRITERIA	SCORE POINTS
Zero	0	No muscular contraction	0
Trace minus or Trace ?	T− or T?	Questionable muscular flicker noted on palpation of muscle when movement attempted	1
Trace	T	Definite contraction or tenseness of muscle noted on palpation, but no movement	2
Trace plus	T+	Definite contraction noted on palpation with just beginning of movement	3
Poor minus	P−	Few degrees of motion with gravity and friction eliminated	4
Poor	P	50% of normal range of motion with gravity and friction eliminated	5
Poor plus	P+	More than 50% of normal range of motion with gravity and friction eliminated and can be done at least 5 times	6
Fair minus	F−	Few degrees of motion against gravity (early fatigue)	7
Fair	F	50% of normal range of motion against gravity performed at least 5 times	8
Fair plus	F+	More than 50% of normal range of motion against gravity performed at least 10 times	9
Good minus	G−	Movement against gravity and slight resistance: Range of motion almost complete and performed at least 5 times	10
Good	G	Movement against gravity and moderate resistance performed at least 10 times without fatigue	11
Good plus	G+	Movement against gravity and marked resistance performed at least 10 times without fatigue	12
Normal	N	Normal range of motion against full resistance (according to age, sex, muscular development)	13

Each of the gradations of strength is given a numerical value in the range from 0 to 13. This permits the derivation, by addition, of a score which serves as an indication of the strength of the paretic part and which can be readily compared with a normal score and with serial scores determined during treatment for the same part. Since this method of scoring does not provide for differences in strength due to size or mass of the various muscles, it was decided to divide the upper and lower extremities into areas containing muscles of the same general size, namely (1) the arm-forearm and the thigh-leg and (2) the hand and the foot. This precludes the possibility of disproportionate weighting of the scores by the numerous, but small, muscles of the hand and foot. Furthermore, it permits ready evaluation of the hand and foot as distinct functional units, a factor of particular importance in the rehabilitation of a hemiplegic patient.

In the upper extremity (including shoulder, elbow, forearm, and wrist) fifteen muscle actions are tested (Chart 1*A*). This makes a possible total score of 195 (15 × 13) in the intact normal person. Similarly, in the hand, twenty-five muscle actions give a total score of 325 (25 × 13). In the lower extremity (Chart 1*B*), thirteen muscular actions of the thigh and leg give a total score of 169 (13 × 13). In the foot, eleven muscle actions give a total score of 143 (11 × 13). Because of the relative slight functional importance of the four lateral toes, the total activity of each toe is considered as one muscular action for the purpose of scoring.

At each examination a ratio is determined as follows: the actual score for the part divided by the maximal score for the part. This represents the residual strength for the part in terms of percentage of the normally expected strength. By subtracting the initial percentage of strength from that obtained at the completion of the period of observation, the gain or loss in percentage of the normal muscle strength for that part is obtained. This represents the percentage of actual improvement. Since the percentage of improvement is limited by the initial degree of muscle strength, it is believed that the ratio of the percentage of actual improvement to the percentage of maximum possible improvement gives a more significant estimate of the gain in muscle strength. This is designated the percentage maximum possible improvement achieved. An example will illustrate this method of scoring:

$$\frac{\text{Observed point score}}{\text{Maximal point score}} = \frac{47}{325} = 14.5 \text{ per cent of normal strength}$$

At completion of period of observation, a numerical value of 235 was obtained for the same hand. $\frac{235}{325}$ equals 72.3 per cent of normal strength. 72.3 per cent − 14.5 per cent equals 57.8 per cent actual improvement toward normal. Maximal improvement toward normal equals 100 per cent − 14.5 per cent = 85.5 per cent. Final improvement equals $\frac{57.8 \text{ per cent}}{85.5 \text{ per cent}} = 67.6$ per cent.

2. Passive range of motion: Passive range of motion is tested by means of a manual goniometer which records the maximal angles of motion at a joint. Motion is carried to a point of severe pain or to the point of limitation by spasm or contractures. Mild pain on motion which could be tolerated by the patient or overcome by repeated passive motion is not used as a limiting point. Motion is recorded in 5 degree gradations. The joints tested include the shoulder, elbow, wrist, hip, knee, ankle, thumb, and fingers. For each joint a normal range of the various motions is known (Chart 2). For example, the normal shoulder joint has a range of 0 to 180 degrees in flexion-extension, 0 to 180 degrees in abduction-adduction, and 0 to 180 degrees in internal and external rotation. By summation, this gives a total maximal range of 540 degrees at the shoulder in all directions.

The observed scores for range of motion at the shoulder, elbow, and wrist are added to give a score for the upper extremity exclusive of the hand. The score for the hand is obtained by adding the score for motions at all the finger joints.

The sum of the scores for the hip, knee, and ankle gives a score for the lower extremity. The toes are excluded from consideration because of their relative functional insignificance. The maximal possible normal score is noted below.*

A ratio between the observed score and the normal score for each region can now be calculated. This represents the percentage of normal passive range of motion.

3. Activities of daily living: An "activities of daily living" chart (Chart 3) has been used by the Department of Physical Medicine and Rehabilitation to record the patient's ability to perform, unassisted, a series of activities which are considered essential for self-sufficiency in daily living. Seventy-eight activities are divided into two main categories, nonwalking and walking (or standing).

The data are recorded in terms of the total gain in the number of activities from the start of treatment to the completion of observation. A percentage improvement is calculated by expressing a ratio of observed number of activities accomplished to the expected number of activities. The final percentage of improvement records the ratio of the percentage of the actual improvement to the maximal possible percentage improvement.

Patients selected for study are placed on the regular program of physiotherapy and rehabilitation advocated by Rusk and his group[1-3] which includes active and passive motion of the affected extremities, ambulation, speech training for the aphasic individual, and the teaching of the activities of daily living, such as personal care, feeding, hand activities, and walking activities. The rehabilitation program for each patient is prescribed by Rehabilitation Service physicians according to individual requirements.

Serial determinations are made of all three modalities by experienced physiotherapists at regular intervals during the course of therapy and observation, and the results are documented. In addition, observations by the physician of the effects of drugs on blood pressure, pulse rate, electrocardiogram, side reactions, and changes, if any, on hemogram and urine are made. Data derived by this method are quantitative and lend themselves readily to statistical analysis.

CONCLUSION

1. An objective method is described to study the effect of drugs and physical therapy on the rehabilitation response of the hemiplegic patient.

2. The method incorporates serial determinations of performance of activities of daily living, passive range of motion, and muscle strength and, in addition, the "double-blind" method of drug or placebo medication with comparable controls.

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*Joint	Maximum Degrees
Shoulder	540
Elbow	330
Wrist	240
Hand	1,335 (includes all finger joints)
Hip	255
Knee	120
Ankle	120

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OBJECTIVE EVALUATION OF PHYSICAL AND DRUG THERAPY IN THE REHABILITATION OF THE HEMIPLEGIC PATIENT

I. A Study of Dihydroergocornine (DHO–180)

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INVESTIGATION of the clinical pharmacology of circulatory diseases of the brain has been stimulated by the development of techniques allowing measurement of the effect of drugs on cerebral hemodynamics.[1-3] Dihydroergocornine methanesulfonate (DHO–180)† has been shown to lower increased cerebrovascular resistance in essential hypertension and in hypertensive cerebrovascular disease.[4] Dihydroergocornine is an alkaloid derivative of ergot formed by hydrogenation of the reducible double bond of the lysergic acid component of the molecule.[5] Pharmacologically, this modified compound has enhanced sympatholytic and adrenolytic properties, but it has little or no direct constrictor action on smooth muscles.[6] In man, it has been shown that Dihydroergocornine has hypotensive as well as sympatholytic properties.[7,8] It was considered possible that these properties of Dihydroergocornine might be valuable in altering the "spasm of contractile elements" and "the persistent constriction of the arteriolar bed" which, in part, constitute the pathology of apoplexy.[9]

The present study was undertaken to determine the effect of the combined use of Dihydroergocornine and physical therapy on the time-course of rehabilitation of the hemiplegic patient as compared with placebo and physical therapeutic means; the objective method of studying and evaluating progress in the hemiplegic patient previously described[10] was used.

MATERIALS AND METHODS

Selection of Subjects.—Twenty patients with hemiplegia of acute or chronic duration were studied, the acute stage being arbitrarily considered as a period up to two weeks after the initial cerebrovascular insult.

Acute cases were selected from admissions to the wards of the Fourth Medical Division of Bellevue Hospital.‡ Chronic patients were chosen from routine ad-

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missions to the Rehabilitation Service of Bellevue Hospital and the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center.

The study was limited to hemiplegia resulting from cerebral thrombosis or embolism. Patients with cerebral hemorrhage were excluded from the study because of the possibility that vasodilatation might promote further cerebral bleeding. Also excluded were patients in whom it was believed that the pathologic process would progress more rapidly than rehabilitation, namely patients with (1) malignant hypertension, (2) severe encephalomalacia, and (3) intractable cardiac insufficiency or failure.

All patients received a complete diagnostic survey including roentgen examination of the heart and lungs, electrocardiograms, urinalysis, blood counts, and blood chemistries. Lumbar puncture was performed when indicated. Before the start of treatment all patients were evaluated, with the methods detailed in a previous paper,[10] by physical therapy and occupational therapy personnel of the Rehabilitation Service with regard to the following modalities: (1) muscle strength, (2) passive range of joint motion, and (3) ability to perform the activities of daily living. The results were recorded by a quantitative method,[10] modified from Dinken,[11] which permitted objective comparison of serial examinations.

Description of the Patients.—The patients were divided into placebo control and DHO–180 treated groups, and selection of successive patients for each group was determined by the chance drawing of slips marked "drug" and "placebo" from a hat. It was deemed desirable to attempt to match the patients with respect to age, sex, and etiology, duration, and severity of hemiplegia, but this was not feasible.

The drug group consisted of thirteen patients, eight male and five female, with an average age of 58 years (range, 39 to 84 years). The diagnosis in twelve patients was cerebral thrombosis, associated with hypertension in ten cases and arteriosclerotic heart disease in one, while syphilitic endarteritis with syphilitic heart disease was the diagnosis in the other. The hemiplegia was right-sided in ten patients and on the left in three. Elapsed time from onset of hemiplegia to start of treatment ranged from two hours to four and one-half months, with nine patients treated within the first nine days. Five patients received oral medication, two received the drug intravenously, and six received both. There were three deaths, three, six, and twenty-five days after therapy was discontinued. All three were acute cases, and although none were comatose at the onset, they all exhibited signs of mental confusion and disorientation and were considered to be critically ill. In each case the drug was discontinued after a trial indicated that no immediate beneficial effects were resulting. The average length of treatment for surviving patients was thirty-eight days. The data relating to the patients are indicated in Table I.

The placebo group consisted of seven subjects, four male and three female, with an average age of 58 years (range, 42 to 78 years). The diagnosis in five patients was cerebral thrombosis, associated with hypertension in four and arteriosclerotic heart disease in one. Cerebral embolism associated with hypertension

and arteriosclerotic heart disease was a probable diagnosis in one case, although thrombosis was not ruled out. Cerebral hemorrhage was a questionable diagnosis in a hypertensive woman whose hemiplegia was of ten and one-half months' duration. The hemiplegia was right-sided in four patients and on the left in three. Elapsed time from onset of hemiplegia to start of treatment ranged from four days to ten and one-half months, with three patients treated within the first six days. Four patients received oral medication, while three received oral and intravenous medication. The average length of treatment was thirty-one days. There were no deaths during the course of treatment. The data are indicated in Table I.

In an attempt to determine the effect of passage of time on the return of function, another series of eighteen patients closely matched regarding age, sex, etiology, and mean duration of time after the cerebrovascular accident, but who had no treatment, was selected from direct admissions to the hospital, and tests of the three modalities were done. These patients had been either at home or in hospitals where no organized program of rehabilitation was carried out prior to admission to the Rehabilitation Service of Bellevue Hospital.

Administration of Medication.—The "double-blind" method of medication[10] was employed, and administration was by both oral and intravenous routes. Chronic hemiplegia patients were started and maintained on oral medication. Initially, DHO–180 was given in doses of 3 or 4 mg. twice daily. Later the dose was increased to 10 mg.[8] twice daily, and this was continued for six weeks. Patients with acute hemiplegia were treated with intravenous medication as soon as they came under observation. The dose in the first patient studied was 0.25 mg. daily, but subsequent patients received 0.5 mg. once daily, and two received 0.5 mg. twice daily. Intravenous medication was continued for seven days and then followed by oral doses of 10 mg. twice daily for the next five weeks. Follow-up evaluations of the three modalities were made at two-week intervals during medication and for varying periods of time up to five months after completion of medication.

In addition to the drug or placebo therapy, all patients were carried on the regular rehabilitation program for hemiplegia as practiced in this department.

RESULTS

Immediate Effects.—In eight patients with acute hemiplegia (two hours' to eight days' duration), DHO–180 was administered intravenously in anticipation that signs of immediate improvement of muscle strength and joint motion, as described by some investigators after stellate ganglion block,[9,12–14] might occur. However, no significant clinical change was observed after the intravenous administration of the drug in these patients.

Final Effects.—

1. Muscle strength: Since the percentage of improvement is limited by the initial degree of muscle strength, it was felt that the ratio of the percentage of actual improvement to the percentage of maximum possible improvement would give an accurate estimate of the gain in muscle strength. This was designated the

TABLE I. CHARACTERISTICS OF HEMIPLEGIC PATIENTS

SUBJECT	SEX	AGE	DIAGNOSIS	ETIOLOGY OF HEMIPLEGIA	SIDE OF HEMIPLEGIA	TIME AFTER EPISODE TREATMENT STARTED	NO. DAYS TREATMENT	NO. DAYS OBSERVATION AFTER DRUG THERAPY COMPLETED	INTRAVENOUS DOSAGE (MG.)		ORAL DOSAGE (MG.)	
									SCHEDULE	TOTAL	SCHEDULE	TOTAL
A. 13 Patients Treated With DHO-180												
Acute Cases												
J. H.	M	61	Cerebral arteriosclerosis	Thrombosis	L	5 hours	42	30	0.5 b.i.d. for 7 days	7	10 b.i.d. for 35 days	700
A. Mc.	F	66	Hypertensive and arteriosclerotic heart disease, diabetes mellitus, carcinoma of colon, subdiaphragmatic abscess	Thrombosis	R	2 hours	7	Died	0.5 b.i.d. for 5 days, once a day for 2 days	6	0	0
B. W.	M	56	Hypertensive heart disease	Thrombosis	R	3 days	25	Died	0.5 once a day for 7 days	3.5	10 b.i.d. for 18 days	360
B. Sm.	F	56	Hypertensive heart disease	Thrombosis	R	5 days	42	60	0.5 once a day for 7 days	3.5	10 b.i.d. for 35 days	700
R. D.	M	49	Hypertensive heart disease	Thrombosis	R	5 days	42	48	0.5 once a day for 7 days	3.5	10 b.i.d. for 35 days	700
A. M.	M	66	Arteriosclerotic heart disease	Thrombosis	R	7 days	43	27	0.25 once a day for 1 day, 0.5 once a day for 8 days	4.25	10 b.i.d. for 34 days	680
W. M.	M	84	Essential hypertension	Thrombosis	R	7 days ?	4	Died	0.5 once a day for 4 days	2.0	0	0
Y. T.	M	69	Hypertensive heart disease	Thrombosis; ? hemorrhage	R	8 days	22	60	0.2 once a day for 1 day, 0.25 once a day for 2 days	0.7	8 b.i.d. for 20 days	320
E. F.	F	59	Hypertensive heart disease	Thrombosis	L	9 days	10	4	0	0	10 b.i.d. for 10 days	200

Chronic Cases												
K. L.	M	54	Hypertensive heart disease	Thrombosis	R	1½ months	48	120	0	0	4 b.i.d. for 34 days, 8 b.i.d. for 14 days	496
B. H.	F	44	Essential hypertension; diabetes mellitus	Thrombosis	R	48 days	42	42	0	0	5 b.i.d. for 9 days, 10 b.i.d. for 33 days	750
E. M.	F	55	Essential hypertension; arteriosclerotic heart disease; diabetes mellitus	Thrombosis	L	60 days	42	150	0	0	10 b.i.d. for 42 days	840
C. T.	M	39	Syphilitic heart disease	Syphilitic endarteritis	R	4½ months	43	150	0	0	4 b.i.d. for 25 days, 6 b.i.d. for 8 days, 8 b.i.d. for 10 days	456

B. 7 Patients Treated With Placebo

Acute Cases												
B. F.	F	46	Essential hypertension	Thrombosis	R	4 days	43	60	0.5 once a day for 7 days	3.5	10 b.i.d. for 36 days	720
D. D.	M	78	Hypertensive and arteriosclerotic heart disease	Thrombosis	R	6 days	11	0	0.5 once a day for 7 days	3.5	10 b.i.d. for 4 days	80
B. N.	M	69	Arteriosclerotic heart disease	Thrombosis	L	6 days	43	0	0.5 once a day for 7 days	3.5	10 b.i.d. for 36 days	720
Chronic Cases												
B. Sh.	M	64	Hypertensive and arteriosclerotic heart disease	Thrombosis	R	2 months ?	42	60	0	0	10 b.i.d. for 42 days	840
R. M.	F	42	Essential hypertension; ? arteriosclerotic heart disease	Thrombosis	L	2½ months	49	72	0	0	4 b.i.d. for 28 days, 8 b.i.d. for 21 days	560
J. K.	M	60	Hypertensive and arteriosclerotic heart disease	Thrombosis	R	88 days	22	37	0	0	10 b.i.d. for 22 days	440
S. D.	F	56	Essential hypertension	? Thrombosis or hemorrhage	L	10 months	8	10	0	0	3 b.i.d. for 8 days	48

TABLE II. MUSCLE STRENGTH* IN TEN HEMIPLEGIC PATIENTS TREATED WITH DIHYDROERGOCORNINE AND PHYSICAL THERAPY

	SUBJECT	ARM AND FOREARM		HAND		THIGH AND LEG		FOOT	
		% NORMAL* BEFORE TREATMENT	IMPROVEMENT† (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)
Acute	J. H.	0.0	12.8	0.0	0.0	0.0	37.3	0.0	0.0
	B. Sm.	15.9	79.3	0.0	84.6	91.8	—43.9	82.6	19.5
	R. D.	0.0	12.8	0.0	2.8	13.0	46.9	0.0	0.0
	A. M.	0.0	19.5	0.0	7.7	0.0	37.3	0.0	0.0
	Y. T.	0.0	11.8	0.0	24.3	0.0	38.4	0.0	0.0
	E. F.	78.4	59.8	61.6	40.1	77.0	77.0	70.0	84.0
Chronic	K. L.	31.3	33.9	14.5	67.6	74.6	25.6	19.6	—8.7
	B. H.	69.2	45.3	62.4	64.1	57.4	43.7	28.0	33.9
	E. M.	3.6	7.5	0.0	0.0	14.0	22.9	0.0	0.0
	C. T.	18.3	43.5	13.5	43.1	47.4	32.3	0.0	4.2
Average for ten patients			*32.6*		*33.4*		*31.7*		*13.3*

*Normal scores for muscle strength in numerical units for the parts of the body are: arm and forearm = 195, hand = 325, thigh and leg = 169, foot = 143.
†Improvement given in percentage of maximum possible improvement.

TABLE III. MUSCLE STRENGTH* IN SEVEN HEMIPLEGIC PATIENTS TREATED WITH PLACEBO AND PHYSICAL THERAPY

	SUBJECT	ARM AND FOREARM		HAND		THIGH AND LEG		FOOT	
		% NORMAL* BEFORE TREATMENT	IMPROVEMENT† (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)	% NORMAL BEFORE TREATMENT	IMPROVEMENT (%)
Acute	B. F.	19.5	79.0	0.0	77.6	43.2	47.9	0.0	0.0
	D. D.	49.7	92.0	1.7	100.0	97.0	100.0	100.0	
	B. N.	0.0	0.0	0.0	0.0	2.4	21.0	0.0	0.0
Chronic	B. Sh.	8.7	21.9	0.0	17.5	32.5	49.0	12.6	23.1
	R. M.	0.0	34.7	0.0	0.0	29.0	42.8	28.0	36.3
	J. K.	0.0	1.0	0.0	0.0	32.5	18.5	0.0	0.0
	S. D.	30.2	3.7	7.4	8.0	52.4	—1.3	23.1	—30.0
Average for seven patients			*33.2*		*29.0*		*39.7*		*4.9*

*Normal scores for muscle strength in numerical units for the parts of the body are: arm and forearm = 195, hand = 325, thigh and leg = 169, foot = 143.
†Improvement given in percentage of maximum possible improvement.

percentage of maximum possible improvement achieved. The method of calculation is described in a previous paper.[10]

The percentages of maximum possible improvement achieved are listed in Tables II and III for both the acute and chronic cases on the drug and placebo. As might be expected in the treatment of an entity like hemiplegia, there is a wide

TABLE IV. PASSIVE RANGE OF MOTION EXPRESSED AS A PERCENTAGE OF THE NORMAL RANGE* IN SEVENTEEN HEMIPLEGIC PATIENTS

EXTREMITY	TREATMENT	ACUTE						CHRONIC			
		J. H.	B. SM.	R. D.	A. N.	Y. T.	E. F.	K. L.	B. H.	E. M.	C. T.
Dihydroergocornine and Physical Therapy											
Arm and forearm	Before	93.5	93.2	100.0	95.5	98.7	99.2	75.2	90.7	82.9	70.7
	After	94.8	88.3	92.6	87.8	59.0	94.3	77.0	77.5	89.6	79.3
	Difference	*1.3*	*−4.9*	*−7.4*	*−7.7*	*−39.7*	*−4.9*	*1.8*	*−13.2*	*6.7*	*8.6*
Hand	Before	100.0	100.0	100.0	100.0	100.0	100.0	86.9	98.9	94.0	100.0
	After	100.0	100.0	100.0	95.5	67.4	100.0	91.0	100.0	98.0	100.0
	Difference	*0.0*	*0.0*	*0.0*	*−4.5*	*−32.6*	*0.0*	*4.1*	*1.1*	*4.0*	*0.0*
Thigh and leg	Before	94.0	97.0	91.9	91.9	94.0	90.9	100.0	87.8	100.0	90.9
	After	95.0	98.0	94.0	87.8	87.8	92.3	91.9	86.8	100.0	85.8
	Difference	*1.0*	*1.0*	*2.1*	*−4.1*	*−6.2*	*1.4*	*−8.1*	*−1.0*	*0.0*	*−5.1*
		B. F.	D. D.	B. N.				B. SH.	R. M.	J. K.	S. D.
Placebo and Physical Therapy											
Arm and forearm	Before	100.0	94.8	100.0				73.4	100.0	89.2	88.3
	After	100.0	100.0	77.0				88.8	93.2	81.5	73.0
	Difference	*0.0*	*5.2*	*−23.0*				*15.4*	*−6.8*	*−7.7*	*−15.3*
Hand	Before	100.0	100.0	100.0				100.0	100.0	86.5	100.0
	After	100.0	100.0	100.0				100.0	100.0	100.0	89.9
	Difference	*0.0*	*0.0*	*0.0*				*0.0*	*0.0*	*13.5*	*−10.1*
Thigh and leg	Before	100.0	97.0	90.9				94.0	100.0	89.9	88.9
	After	99.0	100.0	90.9				91.9	90.9	87.8	71.7
	Difference	*−1.0*	*3.0*	*0.0*				*−2.1*	*−9.1*	*−2.1*	*−17.2*

*Normal ranges in total degrees of motion are:
Arm = (shoulder 540° + elbow 330° + wrist 240°) = 1,110°
Hand = (thumb 195° + fingers 1140°) = 1,335°
Thigh-leg = (hip 255° + knee 120° + ankle 120°) = 495°

variation in the data among the individual patients. However, if averages are calculated for all the drug and all the placebo patients respectively, it is found that in the arm-forearm muscle strength increased 32.6 per cent for patients on the drug and 33.2 per cent for patients on the placebo; for the hand, 33.4 per cent for patients on the drug and 29.0 per cent on the placebo; for the thigh-leg, 31.7 per cent on the drug and 39.7 per cent on the placebo; for the foot, 13.3 per cent on the drug and 4.9 per cent on the placebo. From these data it may be concluded that there is no significant difference in the gain in muscle strength beyond that due to physical therapeutic measures between patients receiving DHO–180 and those receiving placebo.

2. Passive range of motion: A comparison of the range of joint motion (expressed as percentages of the normal range) for the arm-forearm, hand, and

thigh-leg before and after treatment and the percentage difference between the two are listed in Table IV. These figures indicate that during the period of observation in both acute and chronic cases, whether the patients were on DHO–180 or placebo, both increases and decreases occurred, but these were relatively slight in magnitude. Patient Y. T. was the single exception to this where large decreases in range of motion were observed due to severe pain on motion.

TABLE V. SUMMARY OF THE DIRECTIONS OF CHANGE OF PASSIVE RANGE OF MOTION

BODY AREA	10 PATIENTS TREATED WITH DHO-180 AND PHYSICAL THERAPY			7 PATIENTS TREATED WITH PLACEBO AND PHYSICAL THERAPY		
	INCREASES	DECREASES	NO CHANGE	INCREASES	DECREASES	NO CHANGE
Arm-forearm	4	6	0	2	4	1
Hand	3	2	5	1	1	5
Thigh-leg	4	5	1	1	5	1
Total	11	13	6	4	10	7

Table V summarizes the number of "increases," "decreases," and "no changes" in passive range of motion for the two groups of patients. Although decreases in range of motion appear to occur more frequently than increases, this difference is abolished when it is considered that a certain number of joints had complete range of motion to begin with and therefore could not possibly show an increase, whereas they could show a decrease; in other words, there was a greater opportunity for decreases to occur than for increases.

Actually, the data indicate that, in the large majority of instances, passive range of motion was complete or almost complete to begin with, and under the present program of therapy, this state, in general, was maintained. In those cases where significant decreases in range of motion did occur, they may be attributed to the onset of a spasticity in the muscles which decreases the passive range of joint motion with time.

3. *Activities of daily living* (A. D. L.): There were ten patients in the DHO-180 and six patients in the placebo group on whom comparison of the accomplishment in performance of activities of daily living at the time of admission and at the time of discharge could be made. For the DHO-180 group the average number of the total activities of daily living required was 70.8; for the placebo group it was 75.7. On admission the average percentage of normal for the activities of daily living for the DHO-180 group was 33.6 per cent and for the placebo group 21.6 per cent. On discharge it was 80.1 per cent for the DHO-180 group and 75.8 per cent for the placebo group. In percentage of maximum possible gain achieved, the average of the DHO-180 group was 76.2 per cent and for those on placebo, 66.8 per cent (Table VI).

It is apparent that there was marked improvement between admission and discharge in the ability to perform the activities of daily living, but that there is no significant difference in this improvement between the DHO-180 and placebo groups.

TABLE VI. PERFORMANCE OF ACTIVITIES OF DAILY LIVING IN SIXTEEN HEMIPLEGIC PATIENTS

SUBJECTS	TOTAL A. D. L. REQUIRED	A. D. L. ON ADMISSION		GAIN BEFORE DISCHARGE		% OF MAXIMUM POSSIBLE GAIN ACHIEVED
		NO.	% NORMAL	NO.	% NORMAL	
Dihydroergocornine and Physical Therapy						
J. H.	75	16	21.3	59	100.0	100.0
B. Sm.	60	12	20.0	48	100.0	100.0
R. D.	77	5	6.5	50	71.4	69.4
A. M.	77	4	5.2	37	53.3	50.7
Y. T.	77	0	0.0	18	23.4	23.4
E. F.	74	50	67.6	24	100.0	100.0
K. L.	64	50	78.1	10	93.8	71.7
B. H.	62	26	41.9	30	90.3	83.3
E. M.	77	11	14.3	42	68.8	63.6
C. T.	65	53	81.5	12	100.0	100.0
Average			*33.6*		*80.1*	*76.2*
Placebo and Physical Therapy						
B. F.	76	12	15.8	60	94.8	93.8
B. N.	77	11	14.3	44	71.4	66.6
B. Sh.	75	10	13.3	54	85.4	83.1
R. M.	75	12	16.0	57	92.0	90.5
J. K.	75	32	42.7	21	70.7	48.9
S. D.	76	21	27.6	10	40.8	18.2
Average			*21.6*		*75.8*	*66.8*

Statistical tests were applied to the results of all three modalities in order to determine significance of any differences. It did not appear safe to use averages and standard errors because the frequency distributions were not known, and it was doubtful if they would be sufficiently normal to justify such tests.*

Other Effects.—

1. Blood pressure and pulse rate: Although no systematic study was carried out, observations of the effect of DHO-180 on the blood pressure and pulse rate were made in the hypertensive patients. Of six hypertensive patients receiving DHO-180 intravenously, five showed mild decreases in blood pressure (about 20 mm. Hg in systolic pressure and usually less in the diastolic pressure) lasting one to three hours. There was no consistent significant fall in pulse rate. On oral administration, significant effects on blood pressure were not observed.

2. Side reactions: Minor side reactions, i.e., nasal stuffiness, nausea, vomiting, flushing, syncope, and headache, with the administration of DHO-180 have been reported.[7,8] In the present series of thirteen treated patients, only one complained of mild nasal congestion, and one other patient was mildly nauseated on 5 mg. twice daily orally, but was later able to tolerate 10 mg. twice daily. Of

*We are indebted to Dr. Donald A. Mainland, Professor of Biostatistics, New York University College of Medicine, who reviewed the statistical data.

the patients receiving DHO-180 intravenously, only one (J. H.) manifested any side reaction. With the first two doses of 0.5 mg. there was generalized warmth followed by nausea and vomiting within fifteen minutes after the injection. After reduction of dosage to 0.25 mg. for two doses, he was able to tolerate the full dose of 0.5 mg. without reaction. In one patient the drug was discontinued because of marked lethargy, but since this state persisted for three weeks after discontinuation of the drug, it most probably was not caused by the drug.

3. Miscellaneous: There was no effect noted on the hemogram, urinalysis, or electrocardiogram. One patient (B. W.) developed intermittent 2:1 auriculoventricular heart block while receiving DHO-180 orally. However, the arrhythmia persisted after the drug was discontinued, and it was concluded that this was probably not related to the drug.

One patient (J. K.) suffered two episodes of acute coronary insufficiency with transient electrocardiographic changes during the study, and medication was discontinued after the second episode. It was subsequently learned, when the code was broken, that he had been receiving placebo and not DHO-180.

DISCUSSION

The trial of new drugs and procedures in the treatment of the hemiplegic patient needs no justification. Physical therapeutic measures have tended to stress the re-education and strengthening of the musculature that remains functional after the damage inflicted by the cerebrovascular episode. What still remains questionable is whether a justifiable rationale has always been utilized in applying these new drugs and procedures. For the most part, the rationale has been related to the ability of the drugs to produce vasodilatation, but these have apparently been chosen primarily for such effects on vascular structures other than those supplying the brain and therefore indirectly deduced as being useful in altering cerebrovascular hemodynamics.

The technique for measuring cerebrovascular hemodynamics devised by Kety and Schmidt[1] has allowed direct analysis of the effects of drugs and procedures on cerebral blood flow, cerebrovascular resistance, and oxygen and glucose utilization by the brain. By this method, it has been possible to demonstrate that aminophylline, which is a coronary vasodilator, causes a striking and highly significant increase in cerebrovascular resistance which results in a decrease in cerebral blood flow.[15] Aminophylline, in intravenous doses of 0.5 Gm., instead of acting as a vasodilator, produces a marked constriction of cerebral vessels with cerebral anoxia as reflected in the constant and striking decrease in cerebral venous oxygen content.

Nicotinic acid given intravenously to patients with cerebrovascular disease produced no significant changes in cerebral blood flow, oxygen utilization, or cerebrovascular resistance.[16] The same was true for unilateral stellate ganglion block performed on nineteen subjects which included normal subjects and patients with cerebrovascular disease.[17] In three of these patients the stellate ganglia were blocked within two to twelve hours after an acute cerebral thrombosis. In another study bilateral procaine block of the stellate ganglia also produced no

change in cerebrovascular resistance or blood flow.[18] Scheinberg[17] believes that stellate ganglion block might even produce a decrease in cerebral blood flow by directing more blood to the skin and subcutaneous tissues of the face. With these facts in mind, the apparent successes obtained with stellate ganglion block in acute cerebral thrombosis and embolism[9,12-14] may be attributed to coincidence, a factor which is entirely possible in studies with inadequate controls.[19] However, Kety[2] points out that it is still "perfectly possible that reflex cerebrovascular spasm in response to embolism or thrombosis may occur and be mediated by this sympathetic innervation," and this may explain the beneficial effects of this procedure in some instances of acute apoplexy.

Russek and Zohman[20] reported successful management of vascular encephalopathy by the use of large oral doses of papaverine (up to 18 gr. daily). These results were based on observations of forty-six patients with encephalopathy associated with hypertensive disease and cerebrovascular disease without hypertension. The rationale for the use of papaverine was based on the knowledge that (1) papaverine is a coronary vasodilator and (2) in encephalopathic episodes a state of cerebral angiospasm exists. No control studies and no estimation of the central depressant effects of papaverine were made. A clinical corollary exists with the use of papaverine in angina pectoris where an initial report, which was favorable,[21] was later revised when control studies were done.[22] However, a recently reported study of Scheinberg and associates[23] offers more direct evidence to support the rationale and conclusions of Russek and Zohman. The former were able to demonstrate in a group of patients which excluded those with known cerebrovascular disease that intravenous papaverine (180 mg.) resulted in a 24 per cent increase in cerebral blood flow and a 28 per cent decrease in cerebral vascular resistance. This was interpreted as indicating dilatation of cerebral blood vessels. Such studies extended to patients with and without hypertension would be of great interest.

The decision to use DHO-180 in hemiplegia was based on the fact that the drug has been shown to decrease the cerebrovascular resistance in essential hypertension with cerebrovascular disease. It was anticipated that a decrease in cerebrovascular resistance might be obtained which would secondarily provide a greater blood flow to the involved cerebral areas with eventual favorable effects on the affected extremities in the patient with hemiplegia. However, no greater effect on the time-course of rehabilitation was found with DHO-180 than with placebo. A possible explanation of this failure may be that DHO-180 is less effective in reducing cerebrovascular resistance when the cerebrovascular disease is diffuse and associated with organic vascular changes as in the patient with hemiplegia as compared to the patient with essential hypertension with only angiospastic but no organic involvement. Another explanation may be that the reflex spastic phase of involvement of the cerebral vessels was already over by the time the drug was administered. Also to be considered here is the previously described phenomenon of tachyphylaxis,[24] which supervenes with continued administration of this drug.

In spite of the failure of DHO-180 to exert a beneficial effect on the time-course of rehabilitation in the hemiplegic patient, this study demonstrates that a

formal program of rehabilitation does have such an effect. Table VII compares the averages of results of tests in the three modalities of a group of eighteen untreated hemiplegic patients (whose selection has been described earlier in this paper) with the combined group of seventeen patients treated with the rehabilitation program and DHO-180 or placebo. The two groups were studied at an average time of 4.4 and 4.5 months, respectively, after the onset of the hemiplegia. A very striking difference is noted in the results of the activities of daily living (A. D. L.) testing. The untreated patients, on the average, were able to accomplish 33.0 per cent of the activities, whereas the group which had passed through the formal rehabilitation program had an average accomplishment of 78.4 per cent. The treated group also demonstrated a consistently greater muscle strength and range of motion although these differences are less striking than for the activities of daily living.

TABLE VII. COMPARISON OF FUNCTIONAL STATUS IN THREE SERIES OF PATIENTS WITH HEMIPLEGIA AT AVERAGE TIME 4.5 MONTHS AFTER CEREBROVASCULAR ACCIDENT

	AFTER TREATMENT ON REHABILITATION SERVICE			DIRECT ADMISSION TO REHABILITATION SERVICE FROM HOME OR OTHER HOSPITAL (NO TREATMENT)
	WITH DHO-180 AND REHABILITATION PROGRAM	WITH PLACEBO AND REHABILITATION PROGRAM	COMBINED	
No. of patients	10	7	17	18
Average time of analysis after cerebrovascular accident (months)	4.6	4.5	4.5	4.4
A. D. L. (% normal)	80.1	75.8	78.4	33.0
Muscle strength (% normal)				
Arm and forearm	44.3	39.5	41.7	25.6
Hand	40.6	30.0	36.2	22.5
Thigh and leg	60.5	59.2	60.0	39.3
Foot	25.7	26.7	26.1	17.4
Range of motion (passive) (% normal)				
Arm and forearm	84.0	87.6	85.5	81.2
Hand	95.2	98.6	96.6	90.2
Thigh and leg	91.9	90.3	91.3	82.5

It would appear from these facts that although the simple passage of time may result in a certain amount of spontaneous recovery or improvement in some hemiplegic patients, the institution of an active program of rehabilitation definitely has a favorable influence on the prognosis with regard to return of function and particularly to the development of self-sufficiency in the activities essential to daily life.

The analysis of the data in relation to the effect of physical therapy on muscle strength, passive range of joint motion, and the activities of daily living would seem to indicate that the greatest effect of the program of rehabilitation is in re-educating the patient to use more effectively "what he has left" in daily activities

rather than in producing any large increases in muscle strength or range of joint motion of the affected part. This applied, in general, to both the acute and the chronic hemiplegic patients.

It appears that, unless the affected extremities recover muscle strength within the first few weeks, individual muscles recover only slightly in the ensuing months and that the ability of the patient to ambulate satisfactorily is dependent upon the success he has in learning to use the remaining normal muscles. In addition, it has recently been demonstrated by Kabat and Levine[25] that mass muscle movement patterns in the retraining process seem to result in a greater return of muscle function.

In order to explain the failure of DHO-180 to affect appreciably the time-course of rehabilitation, it is possible that in addition to the cerebrovascular effects of the drug the effect on muscle spasticity must be evaluated. Accordingly, the action potentials of the involved leg muscles in a chronic hemiplegic subject were electromyographically analyzed before, during, and after the administration of intravenous DHO-180 and placebo in similar dosage to that used in this study. There was no significant effect of the drug or placebo on spasticity. On the basis of this observation, screening techniques involving the choice of drugs to be used in the treatment of the patient with hemiplegia should include a study of the effect of the drug on cerebral hemodynamics as well as the effect on spasticity.

CONCLUSIONS

1. Using the "double-blind" technique of administration, Dihydroergocornine methanesulfonate (DHO-180) administered in conjunction with a formal program of physical therapy and rehabilitation to ten hemiplegic patients resulted in no significant effect on the time-course of rehabilitation as measured by serial analyses of muscle strength, passive range of joint motion, and activities of daily living when compared with seven other hemiplegic patients given placebo in addition to the program of rehabilitation.

2. Since there was no apparent difference in these two groups, they were combined (seventeen patients) and compared with still another group of eighteen patients closely matched with regard to age, sex, etiology, and mean duration of time after the onset of the hemiplegia, but who had received no specific drug therapy or rehabilitational program. The treated group demonstrated an average accomplishment of the activities of daily living approximately 133 per cent greater than the untreated group. Smaller but appreciable increments in muscle strength and range of motion were also noted for the treated group over the untreated group.

3. The favorable influence of a formal program of rehabilitation on the prognosis in the hemiplegic patient with regard to return of function and the development of self-sufficiency in the activities essential to daily life is demonstrated.

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A CASE OF HEART BLOCK TREATED WITH 1-CYCLOHEXYL-2-METHYLAMINOPROPANE (BENZEDREX)

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THE value of the adrenalin-like group of drugs in the treatment of conduction defects has been well recognized since the reports of Hollingsworth,[2] Stecher,[3] and Wood.[1] Both adrenalin and ephedrine are likely to leave unpleasant side effects when used in effective dosage. Consequently, it seems worth while to report the use of a new sympathomimetic drug which is relatively free from untoward action and which has been found to be remarkably effective in the one patient to whom we have administered it.

J. M. B., a 63-year-old white woman, complained of attacks of faintness. The initial seizure had appeared two months previously while she was at rest in bed. At that time the pulse had been counted, and she had been told that the rate was very slow. She was given an injection of Coramine, and within about ten minutes the sensation of faintness disappeared entirely.

Following this initial episode there had been numerous recurrences, most of which had appeared during mild exercise. The patient was quite observant and had learned to count her own pulse rate. She had found that at rest it was usually about 80, but that slight exertion would often cause the rate to decline to or near 50. At the same time the sensation of faintness would occur. The attacks occasionally appeared at rest, without apparent reason, but could be induced at will by exercise.

The remainder of the history was irrelevant.

The positive physical findings were limited to the heart. The point of maximal impulse was found to be in the fifth left intercostal space in the mid-clavicular line. The second heart sound was distinct in all valve areas, but the first sound was extremely faint, and one had to listen very carefully to hear it at all. There was a barely audible (Grade 1) soft systolic murmur at the apex. The rate was 80 and regular. After exercise, which consisted of ten sit-ups, the heart rate was 50 beats per minute and was again found to be regular. The first heart sound could now be readily heard. The second sound was still distinct, and a third sound appeared in early diastole. Between the second and the third sounds there was a very soft diastolic blow.

The electrocardiogram taken at rest revealed a P-R interval ranging from 0.19 to 0.20 second. There was left axis deviation and intraventricular block. After exercise the QRS complexes remained unchanged, but 2:1 auriculoventricular block appeared, the P-R interval decreasing to 0.16 to 0.17 second (Fig. 1).

The effect of various drugs was then studied. Nitroglycerin was found to induce second-degree heart block, the change occurring when the auricular rate exceeded 90. Although large doses of ephedrine had a favorable effect, they tended to cause tension and nervousness. Smaller doses were ineffective. Since 1-cyclohexyl-2-methylaminopropane (Benzedrex) is an adrenalin-like drug and is relatively free from excitatory action on the central nervous system, this drug was investigated. Rather striking effects were noted. When 2:1 block was already present, the administration of this drug by inhalation (from a Benzedrex inhaler) caused the second-degree block to disappear (Fig. 2).

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Repeated studies of the effect of exercise were made. It was found that when no drugs were administered, a standardized exertion (consisting of standing up and sitting down every three seconds for forty seconds) was sufficient to initiate 2:1 block. When, on the other hand, the same procedure was repeated after several deep inhalations of Benzedrex, the block did not occur (Fig. 3). The onset of the effect was rapid. The duration of the effect of the drug was not studied in detail but was found to be greater than one hour.

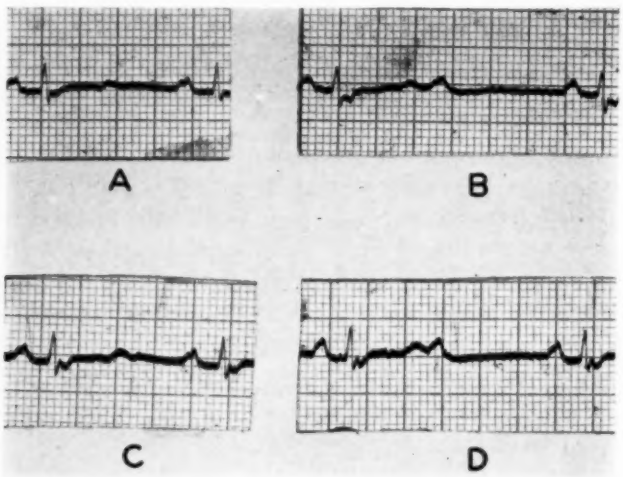

Fig. 1.—*A*, Control record at rest. The P-R interval was 0.19 second, the auricular-ventricular ratio 1:1 with auricular and ventricular rate of 67 per minute. *B*, Second-degree heart block after exercise. The P-R interval was 0.16 to 0.17 second, the ventricular rate 43, and the auricular rate 86. *C*, Control electrocardiogram before nitroglycerin. The P-R interval was 0.2 second, the auricular-ventricular ratio 1:1, and the auricular and ventricular rate 67. *D*, Second-degree heart block after nitroglycerin. The P-R interval was 0.17 second, the auricular-ventricular ratio 2:1, and the ventricular rate 48 per minute.

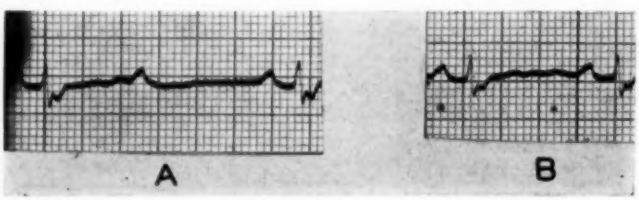

Fig. 2.—*A*, This record reveals second-degree heart block before Benzedrex. The P-R interva was 0.17 second, the auricular-ventricular ratio 2:1, and the ventricular rate 45. *B*, After Benzedrex inhalations the record revealed a normal rhythm. The P-R interval was 0.20 second, the auricular-ventricular ratio was 1:1, and the auricular and ventricular rates were 77 per minute.

Although the use of a rapidly acting drug by inhalation constitutes an excellent method of treatment, it is not ideal from the standpoint of prevention because of the uncertainty of dosage. Consequently, an attempt was made to control the symptoms by administering 1-cyclohexyl-2-methylaminopropane (Benzedrex) orally.* The results were highly gratifying. For the past four and one-half months the patient has taken two to three Benzedrex tablets a day (each containing 50 mg.) and has not experienced a single episode of bradycardia. The blood pressure has remained within normal limits, and she has not experienced any symptoms of central nervous

*We are indebted to Mr. T. B. Wallace, Smith, Kline & French Laboratories, Philadelphia, Pa., or supplying the Benzedrex used in this study.

system stimulation, such as nervousness, jitters, or sleeplessness. She has continued normal activity and has not had to restrict her activities in any way.

Three points seem worthy of comment:

1. Although calcification of the mitral valve was not demonstrated, the combination of heart block with apical systolic and diastolic murmurs makes it altogether likely that the underlying lesion was fibrosis of the mitral annulus, with involvement of the bundle of His (Rytand's syndrome[4,5]).

2. The appearance of syncopal symptoms on exertion occurs under a number of circumstances. Aortic stenosis is perhaps the most common cause.[6-8] However, the only condition in which syncope, attended by a sudden bradycardia, occurs regularly on exertion is second-degree heart block. The diagnosis may, therefore, be made from the history alone if, as in this instance, the patient is cognizant of the bradycardia.

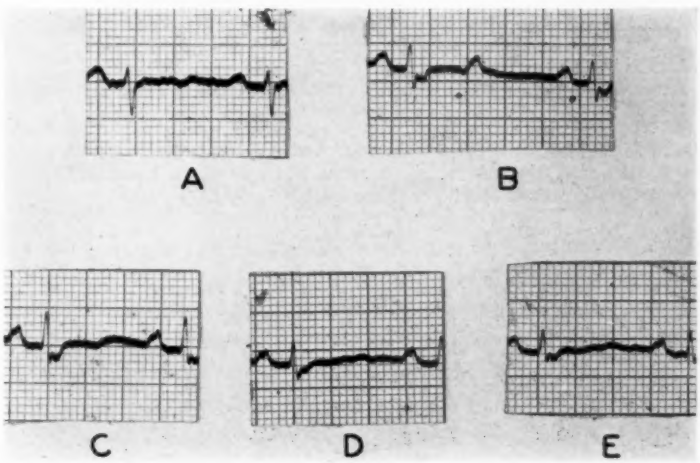

Fig. 3.—*A*, This record was taken before exercise and before Benzedrex. The P-R interval was 0.19 to 0.20 second. The auricular-ventricular ratio was 1:1, and the auricular and ventricular rate was 81 per minute. *B*, This record was taken after exercise but before Benzedrex. Note the development of second-degree heart block. The P-R interval was 0.17 second. The auricular-ventricular ratio was 2:1, the ventricular rate was 62, and the auricular rate was 124. *C*, This record was taken immediately after exercise, fifteen minutes after Benzedrex inhalation. Two-to-one heart block did not develop. The P-R interval was 0.2 second. The auricular-ventricular ratio was 1:1, and the auricular and ventricular rate was 81 per minute. *D*, Immediately after exercise, thirty minutes following Benzedrex inhalation. This record shows essentially the same findings as *C*. *E*, Immediately after exercise, one hour following Benzedrex inhalation. Two-to-one heart block is still absent. Findings are essentially as shown in *C* and *D*.

3. The management of Adams-Stokes attacks involves two different but related problems: (a) emergency treatment with quick-acting drugs to increase the heart rate during the seizures and (b) continued treatment with slow-acting drugs to prevent the seizures. In our patient 1-cyclohexyl-2-methylaminopropane has been an almost ideal drug because of the rapid onset of effect when utilized by inhalation and the long duration of action when administered orally. The drug has thus far been gratifyingly free of stimulation of the nervous system and of other undesirable side effects.

SUMMARY

The patient reported apparently had fibrosis of the mitral annulus. Measures which increased the auricular rate (exertion, nitroglycerin) caused the development of mild Adams-Stokes seizures with 2:1 heart block and faintness, but without syncope or convulsions. The attacks responded quickly to the inhalation of 1-cyclohexyl-2-methylaminopropane (Benzedrex) and have apparently been effectively prevented by the oral use of the same drug.

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TUBERCULOUS PERICARDITIS

A Study of Forty-One Cases With Special Reference to Prognosis

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WHEN pericarditis occurs as the primary clinical manifestation of tuberculosis, physicians have justly asserted for many years that the prognosis is grave. Clinicopathological studies, stimulated by the classic descriptions of Osler, Riesman, and others,[1-4] have established the viewpoint that this relatively rare complication usually arises by extension from a neighboring tuberculous focus, most commonly from the hilar lymph nodes. Less important, because it does not modify the underlying disease process, is hematogenous seeding of the pericardium in miliary tuberculosis. Primary invasion of the pericardium by acid-fast organisms is extremely rare,[11,26] and some observers[12] state that it does not occur.

Once infection is established, an initial inflammatory reaction ensues, characterized clinically by dyspnea, precordial pain, and a pericardial friction rub. Pericardial effusion almost invariably accompanies this reaction, at times culminating in cardiac tamponade. Should the patient survive, the effusion eventually disappears, but often there remains a thickened, granulomatous pericardium which, of itself, can cause cardiac dysfunction. The granulation tissue may heal, leaving a residuum of dense fibrosis which occasionally produces the clinical triad of a small, quiet heart, peripheral edema, and ascites.

Only rarely is the entire natural history of clinically primary tuberculous pericarditis observed in a single case. Frequently the patient dies in the early stages of the disease, either from cardiac embarrassment or extrapericardial or miliary tuberculosis. When the effusion is resorbed, some patients apparently make a complete clinical recovery. Less frequently, the disease is first observed in the phase of pericardial constriction. An occasional case of tuberculous pericarditis may occur without localizing symptoms and is first discovered on postmortem examination.

The grave prognosis has been emphasized by all who have studied this disease. Clarke[5] reported nine deaths in a series of thirteen cases, with follow-up periods ranging from three to twenty-three months. Thompson[6] emphasized the extremely poor outlook for patients over 50 years of age. Harvey and Whitehill[7] reported a mortality of 80 per cent in thirty-seven proved cases but of only 5.9 per cent in thirty-four presumptive cases of tuberculous pericarditis.

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Eighty per cent of their patients were Negroes, and follow-up periods ranged from six months to seven years. Keefer,[8] in a study of twenty cases, reported that eighteen patients were dead within one year after the onset of symptoms, and Stepman and Owyang,[9] in a series of thirty-seven, could find only 8 per cent alive after two years. Andrews, Pickering, and Sellors[10] reported eleven deaths in a group of sixteen cases followed over a five-year period.

The extent to which chemotherapy may influence mortality statistics in this disease is a matter of speculation. Preliminary reports[13,14] on the use of streptomycin are optimistic, but follow-up periods are still too short to permit full evaluation. To aid in the appraisal of the outlook for patients suffering from tuberculous pericarditis and to assist in the future evaluation of the effects of modern methods of chemotherapy, the experience of this hospital with tuberculous infection of the pericardium has been reviewed. Special efforts were made to ascertain which features of the disease were of prognostic value.

MATERIAL

The material for study consisted of twenty cases collected from the autopsy files covering the period 1910 to 1950. Twenty-one additional cases were selected from the clinical files for the two decades between 1930 and 1950. Five more autopsied cases were discarded because the pericarditis occurred in the terminal phase of miliary tuberculosis. One additional patient died of other causes, and an old, tuberculous, constrictive pericarditis was first demonstrated at the autopsy table. Of the forty-one acceptable patients, twenty-seven were dead and fourteen were alive at the time of the last follow-up examination. In twenty of the deceased the cause of disease was proved by post-mortem examination, and in three others tubercle bacilli were demonstrated in fluid removed from the pericardium during the acute stage. The evidence for tuberculosis in the four remaining cases was: past history of proved tuberculosis, one; probable tuberculous peritonitis and a strongly positive intradermal tuberculin test, one; recent, prolonged exposure to tuberculosis and a strongly positive tuberculin test, one; Addison's disease due to adrenal tuberculosis, one.

Evidence for tuberculosis as the cause of pericarditis was good in seven of the living patients (i.e., pericardial or extrapericardial tuberculosis demonstrated at the time pericarditis developed). The evidence in these seven living "presumptive" patients consisted of: strongly positive tuberculin test in individuals in whom work-up was otherwise negative, four; pulmonary infiltrates having the appearance of tuberculosis, two; past history of proved tuberculous cervical adenitis, one. Follow-up studies were performed on ten of the living patients, and the clinical status was evaluated by physical, roentgenological, and electrocardiographic examinations.

The age and sex incidences are listed in Table I. Five of the female patients were white. In four patients the serological test for syphilis was positive, and three of these had received specific treatment. One patient had rheumatic heart disease, and another had hypertension. There was no evidence of myocardial infarction in any instance in this series.

TABLE I. DISTRIBUTION ACCORDING TO AGE AND SEX

AGE AT ONSET (YEARS)	SEX		TOTAL
	MALE	FEMALE	
Under 9	2	1	3
10—19	4	2	6
20—29	2	0	2
30—39	3	3	6
40—49	6	3	9
50—59	6	1	7
60—69	4	1	5
70 and over	3	0	3
Total	30	11	41

History.—The onset of symptoms was sudden in nine cases and gradual in twenty-eight. Four patients had no localizing symptoms, and pericarditis was first discovered at autopsy. It is interesting to note that ten patients had prodromal symptoms simulating a respiratory infection. Similar prodromata occur with greater frequency in acute serofibrinous pericarditis as reported by Levy and Patterson[15] and Carmichael and associates.[16] The presenting symptoms varied considerably in different patients, and no characteristic pattern could be discerned. Twenty-five complained of dyspnea, sixteen had precordial pain, and three had pain in the left shoulder. Seventeen suffered from fever, thirteen noted peripheral edema, and eleven complained of loss of weight. Similar symptomatology was noted by Harvey and Whitehill in approximately the same order of frequency.[7] Two patients were first observed with full-blown symptoms of Pick's disease.

The duration of symptoms before the patients were seen by a physician was also subject to marked variation. Six patients complained of symptoms for less than one week, eleven for one to four weeks, five for one to two months, nine for three to five months, six for six to twelve months, and one patient was not seen until two years after the onset.

Physical Examination.—The physical findings on admission are summarized in Table II. In addition to those listed, three patients had hypertension and four had hypotension. Roentgenograms of the chest were made in thirty-seven cases. The heart was enlarged in twenty-eight, and pericardial effusion was apparent in fourteen. Congestive failure was a prominent feature in twenty-eight cases, and pleural effusions were present in fourteen.

Laboratory Findings.—Pertinent laboratory data are listed in Table III. Measurements of circulation time and vital capacity were made too infrequently to be meaningful. Blood cultures were drawn in twenty-four cases, and all were negative. Three of the patients in whom the leucocyte count was greater than 15,000 were in the first decade of life.

Electrocardiograms.—Thirty-four patients were followed during the course of their illness with serial electrocardiograms. In only two did the records re-

main normal during the course in the hospital. T-wave negativity was found in twenty-five cases, low voltage in eleven, and RS-T elevation in only five instances. These findings are somewhat at variance with those usually reported in acute pericarditis. Paroxysmal auricular fibrillation occurred in four cases, and permanent auricular fibrillation was present in three others. Auricular flutter and premature ventricular extrasystoles each occurred once. It is perhaps significant that all the patients in whom an arrhythmia was observed are dead and that none of the living patients has suffered such an abnormality. Other findings included prolonged atrioventricular conduction in three cases and left bundle branch block in two others. These latter abnormalities were confined to individuals more than 50 years of age and hence may be best accounted for by the presence of coronary sclerosis.

TABLE II. CLINICAL FEATURES ON ADMISSION

PHYSICAL FINDING	NUMBER OF CASES
A. Fever	
None	7
Less than 100° F.	4
100°—101.9°	16
102°—103.9°	13
104° or over	1
B. Pulse	
Less than 80	4
81—99	9
100—119	16
120—139	9
140 or over	3
C. Heart	
Not enlarged (percussion)	10
Enlarged	31
Heart sounds	
Normal	18
Muffled	20
Gallop	5
Murmurs	
None	30
Systolic	11
Diastolic	2
Pericardial friction	
None	26
Present	15
Pericardial effusion (x-ray)	
None	23
Present	14

Course.—In the hospital the temperature usually varied daily between 100° F. and 103° F. and returned to normal ranges concomitant with recovery or continued its swinging course as the patient's condition grew worse. The duration of the period of hospitalization varied widely. Among the fourteen living patients only one remained for less than two weeks, eleven remained for periods ranging from two to twelve weeks, and two remained for more than three months. Of the twenty-seven fatal cases, sixteen died of tuberculous pericarditis (seven with

effusion), three of miliary tuberculosis, two of gastrointestinal tuberculosis, one of tuberculous bronchopneumonia, and one during attempted pericardiectomy. Three deaths were classified as being of cardiac origin; autopsies were not performed in these cases.

TABLE III. LABORATORY DATA

LABORATORY VALUE	NUMBER OF CASES
A. Hemoglobin	
Normal	20
Anemia	21
B. Leucocytosis	
None	20
10-14 thousand	17
15-20 thousand	3
Over 20 thousand	1
Polynucleosis	8
Lymphocytosis	2
C. Sedimentation Rate (Westergren Method)	
Elevated	27
Normal	4
Not done	10
D. Venous Pressure (mm. saline)	
Less than 100	3
100-149	10
150-199	6
200-299	7
Not stated	15
E. Pericardial Fluid	
Not obtained	33
Examined	8
Specific gravity	
Less than 1.018	2
1.018 or over	6
Leucocyte count	
Not done	1
Under 500	0
500-999	1
1000-1999	1
2000-4999	3
Over 5000	1
Polynucleosis	0
Lymphocytosis	6
Red cells present	8
Tubercle bacilli demonstrated in fluid	4

Six of the patients who died developed constrictive pericarditis. In all there was a gradual onset of symptoms. The duration of symptoms varied from one to four weeks in two, two survived three to five months after the onset, and one was not seen by a physician for two years after the onset. The sixth patient, who died during pericardiectomy, was observed for eight years after the acute episode before developing Pick's syndrome. In this group, symptoms progressed steadily after the onset, and no asymptomatic period occurred between resorption of the effusion and the development of constrictive pericarditis.

On the other hand, none of the living patients has developed clinically obvious constrictive pericarditis. Nine are asymptomatic, two have developed pulmonary tuberculosis, and one has developed tuberculous endometritis after five years of apparent good health. Two of the living patients had obvious Pick's disease and were found to have tubercles in the tissue removed at pericardiectomy. In these two cases no history suggestive of the earlier phases of tuberculous pericarditis could be obtained, and each is doing well after operation. The duration of the follow-up period in each case is shown in Table IV.

TABLE IV. DURATION OF FOLLOW-UP PERIOD

DURATION OF FOLLOW-UP (YEARS)	LIVING		DEAD	
	PROVED	PRESUMPTIVE	PROVED	PRESUMPTIVE
Less than 1	2	1	17	2
1–2	1	3	0	0
2–3	2	0	2	1
3–4	0	0	2	0
4–5	0	0	0	0
5–7	1	1	0	1
7–10	0	0	2	0
10–15	1	2	0	0

Autopsy Findings.—Of the twenty autopsied patients, complete records were available in seventeen. Fifteen died of tuberculous pericarditis; six showed effusion and six constriction. Calcification of the pericardium was observed once. The hilar nodes were involved in seven cases, pulmonary tuberculosis was present in seven, and the pleura were involved in five. Tubercles were found in the liver and spleen four times, tuberculous infection of the gastrointestinal tract occurred three times, and the kidneys and adrenals each were involved twice. Terminal miliary seeding was demonstrated in four patients. The heart was enlarged in ten. In the constrictive group the heart was enlarged in four cases, and in two it was normal in size. This demonstration of an enlarged heart in constrictive pericarditis is at variance with the classical concept of the small quiet heart seen in Pick's syndrome. Myocardial tuberculosis was observed twice and coronary sclerosis four times. All except three of the seventeen patients were free of valvular disease, and no patient showed evidence of myocardial infarction.

DISCUSSION

Allowance for differences in hospital population and duration of follow-up periods being made, the clinical aspects of tuberculous pericarditis in this series are, in a general way, quite similar to those described by Harvey and Whitehill,[7] Andrews, Pickering, and Sellors,[10] and others[5,8,9] and hence will not be discussed further. With a mortality of approximately 50 per cent in the first year after the onset of symptoms, pericarditis is obviously a grave manifestation of tuberculosis. Although this fact has been implicit in all considerations of the disease, the factors

affecting the prognosis have not been fully stated. Admittedly, it is impossible in a study of this sort to evaluate the crucial influences of bacterial virulence and host resistance. Nevertheless, several clinical points of prognostic value may be derived from the data presented. In order of importance the significant factors include age, mode of onset, occurrence of cardiac arrhythmias during illness, and positive proof of tuberculosis as the etiological agent. Conversely, no prognostic value can be attached to the presence of a pericardial rub, pericardial effusion, or congestive failure.

A. Age.—Among the deceased, ten of the nineteen patients who lived less than one year were over 50 years of age, and none over 50 years lived more than five years. Of the living, only two were over 50 years, and these have been followed less than two years.

B. Mode of Onset.—The deceased patients with a gradual onset of symptoms or those who were without localizing symptoms did less well than those with an acute onset. Of the nineteen deaths occurring in the first year, fifteen had a gradual onset, three were without localizing symptoms, and one patient had a sudden onset of symptoms as a complication of long-standing, relatively quiescent Addison's disease.

With this in mind, the fourteen living patients were reviewed and found to fall into two groups of equal size. Those with sudden onset were younger, spent less time in the hospital, and have been followed for longer periods than those in whom the onset of symptoms was gradual. It is also worthy of note that two-thirds of the patients with sudden onset were Negroes, whereas all but one of those with gradual onset were white.

C. Occurrence of Arrhythmia.—With the exception of one patient, who lived eight years, all in whom cardiac arrhythmias occurred died within six to twelve months after onset. No arrhythmia was noted in any of the living patients. The types of arrhythmias noted were: auricular fibrillation, 7; auricular flutter, 1; frequent premature ventricular contractions, 1.

D. Positive Proof of Tuberculosis as the Etiological Agent.—Harvey and Whitehill noted that 80 per cent of their patients with proved cases died whereas only 5.9 per cent of those with presumptive cases died. In this series thirty of thirty-seven with proved cases (77 per cent) died, and four of eleven with presumptive cases (37 per cent) died. From these data it would seem that proof of tuberculosis markedly decreases the chances for life and consequently is of significant prognostic value. As a corollary to this observation, Peel[12] has emphasized the grave significance of finding tubercle bacilli in the pericardial fluid. These were recovered from the fluid obtained in four of the eight pericardial paracenteses performed in this series. Three of these patients died in less than one year; the one living patient has been followed for less than one year.

The presence of a pericardial rub, pericardial effusion, or congestive failure was of no value in forming an opinion as to prognosis. Patients were found in each follow-up period in whom one or more of these findings had been observed, and several have been followed for as long as seven to ten years.

SUMMARY

1. A study has been made of forty-one cases of clinically primary tuberculous pericarditis. Relevant clinical and laboratory data have been presented. Special attention has been devoted to those clinical features which appear to be of prognostic significance.

2. The prognosis may be considered grave in the presence of advanced age (over 50 years), a gradual onset of symptoms, the occurrence of cardiac arrhythmias, and positive proof of tuberculous etiology. No prognostic significance may be given to the presence of a pericardial friction rub, pericardial effusion, or congestive failure.

3. The mortality rate in the first year after the onset of symptoms is approximately 50 per cent.

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THE USE OF VINYL PLASTIC TUBING IN RECORDING PRESSURE PHENOMENA

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CERTAIN types of pressure recording apparatus employed in cardiac catheterization utilize lead tubing, since the physical characteristics of this metal render it adaptable to such a purpose. There are several objections, however, to lead tubing. It is heavy and difficult to handle and will break at points which are subjected to repeated bending. For the past seven months we have employed vinyl plastic tubing in recording intracardiac and peripheral arterial pressures and have found it more satisfactory than lead tubing in every respect.

The tubing which we have used has an over-all diameter of 0.262 inches and a 0.073 inch bore. It is equipped with standard fittings and is coated with woven nylon. The volume displacement does not change, however, if the nylon is eliminated, and it now seems preferable to leave the tubing uncoated as it may then be cleaned more easily. Various lengths, complete with appropriate fittings, are now available commercially* and are relatively inexpensive.

Pressure curves are obtained which are identical with those registered with lead tubing. The plastic is of light weight and can be easily handled. Its flexibility is considerably greater than that of lead, and it does not break at stress points. It withstands wide temperature variations and can be boiled or autoclaved. It is nontoxic. *It undergoes no measurable volume change for a pressure change of 400 mm. Hg.*

Fig. 1 illustrates brachial artery pressures taken on the same patient using different lengths of lead and vinyl plastic tubings. Tracings were obtained with a Sanborn electromanometer and Poly-Viso Cardiette. An indwelling arterial needle was left in the brachial artery and manipulated as little as possible. The same manometer was used throughout the procedure, and its standardization was checked before and after each tracing. The tubing between the arterial needle and the manometer was changed after each strip had been recorded. The figures shown in the illustration were obtained by averaging the blood pressure values over two respiratory cycles.

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Fig. 2 illustrates the arrangement we use for recording arterial pressures. The tubing from the heparin syringe to the stopcock is also vinyl plastic, although of much smaller caliber than the manometer tubing. With this setup, arterial

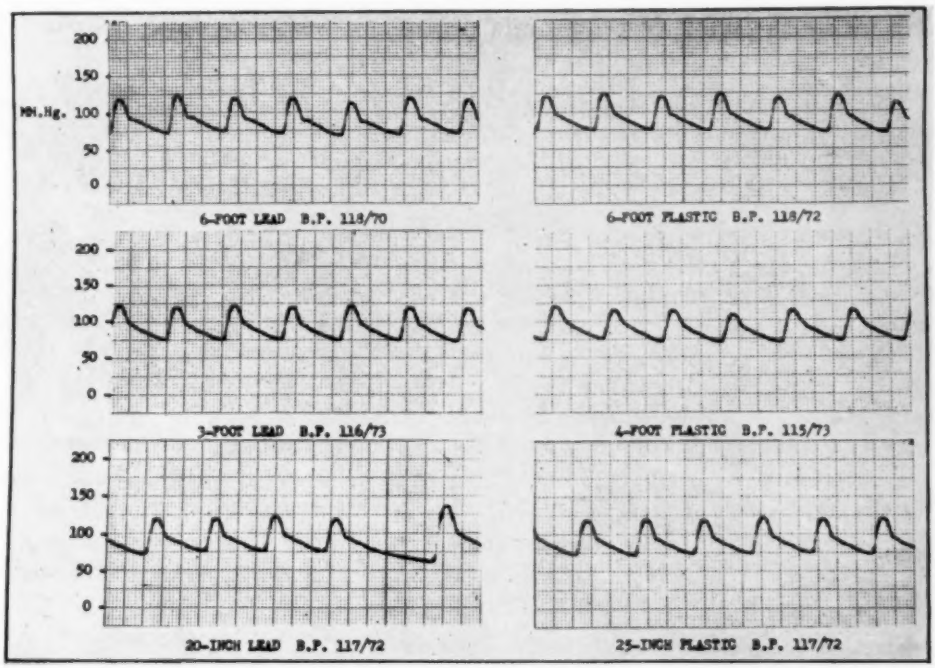

Fig. 1.—Brachial artery pressure recorded through lead and vinyl plastic tubing.

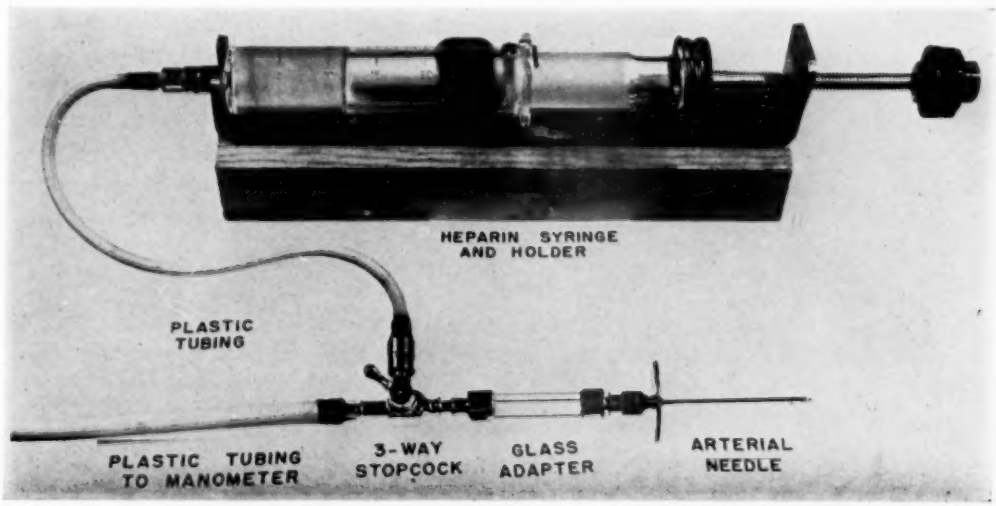

Fig. 2.

pressures can be recorded over long periods of time. To prevent clotting in the needle, the stopcock is turned at intervals, and enough heparin to fill the needle is injected. The syringe holder prevents blood from being forced back into the adapter.

A similar arrangement is utilized with the cardiac catheter. In place of the syringe and holder, however, an ordinary saline infusion to which heparin has been added is connected directly to the sidearm of the stopcock.

We are indebted to Mr. M. B. Rappaport, Senior Research Engineer, Sanborn Co., Cambridge, Mass., for determining some of the physical characteristics of the vinyl plastic tubing and for his helpful suggestions.

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PURULENT PERICARDITIS DUE TO HEMOPHILUS INFLUENZAE, TYPE B

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PURULENT pericarditis is a rare complication of various infectious diseases. It is of clinical importance as it is commonly overlooked in the early stages of development and is almost always fatal if not treated.

Galen first described purulent pericarditis in animals in the second century A.D. and postulated its occurrence in man. Its actual existence in man was not demonstrated until more than a thousand years later. Presumably, no cures were effected until 1844 when Hilsmann performed the first successful pericardiotomy for pyopericardium.[1] Thereafter, this operation afforded a 50 per cent recovery rate in the hands of most surgeons. On reviewing the literature, we found 265 patients so treated up until 1940.[2]

The incidence of purulent pericarditis has decreased considerably with the advent of the general use of antibiotics for the control of pyogenic infections in the early stages. This was demonstrated by Griffith and Wallace in their survey of 13,353 consecutive autopsies performed in the Los Angeles County Hospital during the seven years 1940 through 1946.[3] The disorder still occurs, however, and, as may be expected, is often due to organisms not sensitive to the more commonly used antibiotics. These include the resistant strains of streptococci, staphylococci, and pneumococci, as well as the less frequently encountered *Bacterium tularense*, *Klebsiella pneumoniae*, *Hemophilus pertussis*, and *Hemophilus influenzae*.

Because of the serious nature of the disease, its relative rarity, and the increasing availability of effective therapeutic measures, the following case of purulent pericarditis due to *H. influenzae*, Type B, is reported.

CASE REPORT

A 4-year-old white boy was admitted to the Virginia Mason Hospital on June 20, 1949, because of dyspnea and pain in the upper abdomen of two days' duration. He was the elder of two male children of healthy parents and was a normal infant at birth. He had none of the usual

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childhood diseases and had shown a healthy development until the onset of the present illness. On June 14, 1949, he suffered a bee sting on the left foot, and on the same day he developed a sore throat with a temperature of 101° to 102° F. On June 16, the sore throat had subsided, but he was listless and had anorexia. On June 18, he developed dyspnea and an expiratory grunt and complained of upper abdominal pain. On the following day he vomited several times. On June 20, dyspnea was more marked, and he was hospitalized by the family physician.

On admission he was found to be well developed and well nourished, with a flushed face and obvious dyspnea and expiratory grunt, but no stridor. The temperature was 103° F., pulse, 120 per minute, and the respirations, 26. The tonsils were hypertrophic and inflamed, and the cervical nodes were enlarged and tender. There were diminished breath sounds, moist râles, and dullness over the lower left lung, and a pleural friction rub was heard in the left anterior chest. The heart sounds were normal. The abdomen was soft and nontender.

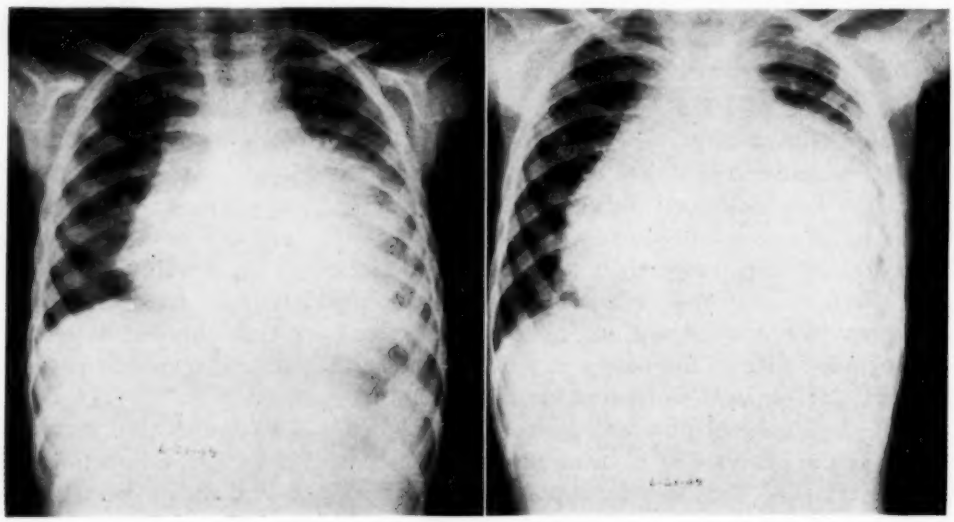

Fig. 1. Fig. 2.

Fig. 1.—Roentgenogram of chest on admission showing pericardial effusion and consolidation of lower lobe of left lung with left pleural fluid.

Fig. 2.—Roentgenogram of chest after seven days of parenteral penicillin therapy showing massive pericardial effusion.

Laboratory examinations showed a leucocyte count of 32,000 with 4 per cent lymphocytes, 5 per cent monocytes, 82 per cent polymorphonuclear neutrophils, and 9 per cent stab cells. The erythrocyte count was 4,890,000, and the hemoglobin was 13.2 Gm. The urinalysis was normal. X-ray examination of the chest (Fig. 1) showed generalized enlargement of the heart shadow with dense, pneumonic consolidation of the lower lobe of the left lung and a moderate amount of fluid in the left pleural space.

Initial therapy included continuous oxygen by tent, 30,000 units of penicillin intramuscularly every three hours, and 300,000 units of procaine penicillin intramuscularly twice daily. After seven days the fever diminished, but dyspnea persisted, and the pulse remained around 120 per minute. A nonproductive cough developed, and the liver became enlarged and tender.

The patient was first seen in consultation by the authors on the eighth hospital day (June 28, 1949), at which time he appeared critically ill. Fluoroscopic and x-ray examination of the chest (Fig. 2) showed a massive pericardial effusion. An electrocardiogram (Fig. 3,*A*) showed only sinus tachycardia. A pericardial paracentesis in the left fifth interspace near the mid-clavicular line, produced 200 c.c. of thin, cloudy, light yellow purulent material. Three hundred thousand units of penicillin were instilled into the pericardial sac. Following the procedure, the patient's color

and respiration improved, and the blood pressure rose from 100/60 to 122/78 mm. Hg. An x-ray examination of the chest showed that considerable fluid remained, and the next day a pericardiotomy was performed (F. J. J.).

The left fifth costal cartilage was resected, and incision into the pericardium resulted in a geyser of greenish-yellow purulent material, approximately 500 c.c. of which were removed. A large amount of soft fibrin covering both pericardial layers was removed by irrigation. Two small, soft rubber drains were left in the pericardial space. Electrocardiograms made continuously throughout the procedure showed an electrical alternans but no other significant abnormalities.

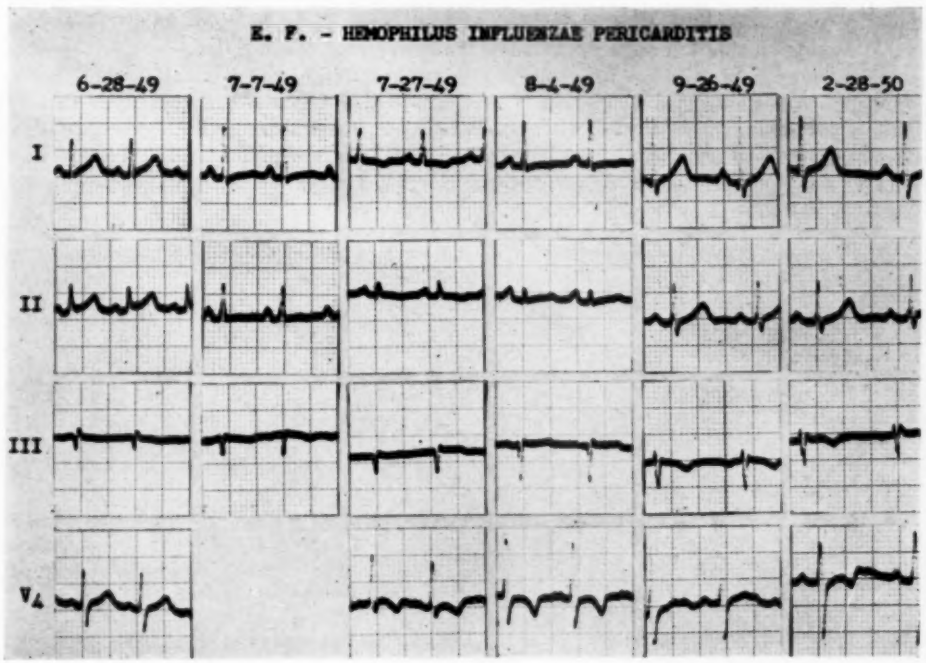

Fig. 3.—Electrocardiograms. *A*, Day before pericardiotomy when purulent pericardial effusion was massive; no specific abnormalities. *B*, Eighth postoperative day at time of increasing edema formation; isoelectric T waves. *C*, Twenty-eighth postoperative day at time of bilateral pleural effusions; inversion of T_1 and T_{V4}. *D*, Thirty-sixth postoperative day at time of recession of edema; isoelectric T_1 and upright T_2 and T_3. *E*, Eight weeks after final discharge; further changes toward normal. *F*, Seven months after final discharge; normal tracing for 5-year-old child.

The day following this procedure, *H. influenzae*, Type B, was isolated from the aspirated purulent material, and dihydrostreptomycin, 1 Gm. daily, was administered, along with a combination of sulfadiazine and sulfamerazine, 2 Gm. daily. The following day, aureomycin 1 Gm. daily was started, and subsequently increased to 2 Gm. daily. By the third postoperative day the patient's temperature, which rose to 103° F. postoperatively, returned to normal levels. The pulse remained at about 120 per minute. All medications were discontinued on the fifth and sixth postoperative days because of periodic vomiting. A 250 c.c. blood transfusion increased the erythrocyte count from 3,800,000 to 5,600,000.

Moderate swelling of the face and feet, increased hepatomegaly, and evidence of fluid in the left pleural cavity were detected on the eighth postoperative day. An electrocardiogram on the same day (Fig. 3,*B*) showed isoelectric T waves in standard and unipolar limb leads. On the thirteenth postoperative day, a left thoracentesis produced 220 c.c. of slightly cloudy, yellow fluid, a culture of which was later reported as sterile. The peripheral edema persisted. The

patient became a feeding problem and was discharged from the hospital on the fifteenth post operative day with the hope that the home environment might correct this. Upon discharge, he had been afebrile for thirteen days. He remained weak, however, and the pulse consistently ranged between 110 and 140 per minute.

The patient was readmitted to the hospital (July 25, 1949) after ten days at home because of progressive enlargement of the abdomen, swelling of the feet and legs, and increased difficulty in breathing. The admission temperature was 99° F., pulse, 110 per minute, and respirations, 20. Blood pressure was 108/70 mm. Hg. The patient was moderately dyspneic and orthopneic. There was evidence of fluid in both pleural cavities, obscuring the heart borders. The heart sounds were of moderately good quality. The abdomen was moderately distended with fluid, and the liver was tender and palpable 4 fingerbreadths below the right costal margin. There was pitting edema of the lower portion of the body up to the nipples. Blood and urine examinations were normal. The erythrocyte sedimentation rate was 2 mm. in one hour. X-ray examination of the chest (Fig. 5) showed fluid in both pleural cavities. An electrocardiogram (Fig. 3,*C*) showed low voltage and inversion of T_1, T_2, and T_{AVL}, inversion of T_{V_1} through T_{V_6}, and depression of ST in V_3 and V_4. Venous pressure determinations were 240 mm. of water in the femoral vein and 320 mm. of water in the antecubital vein.

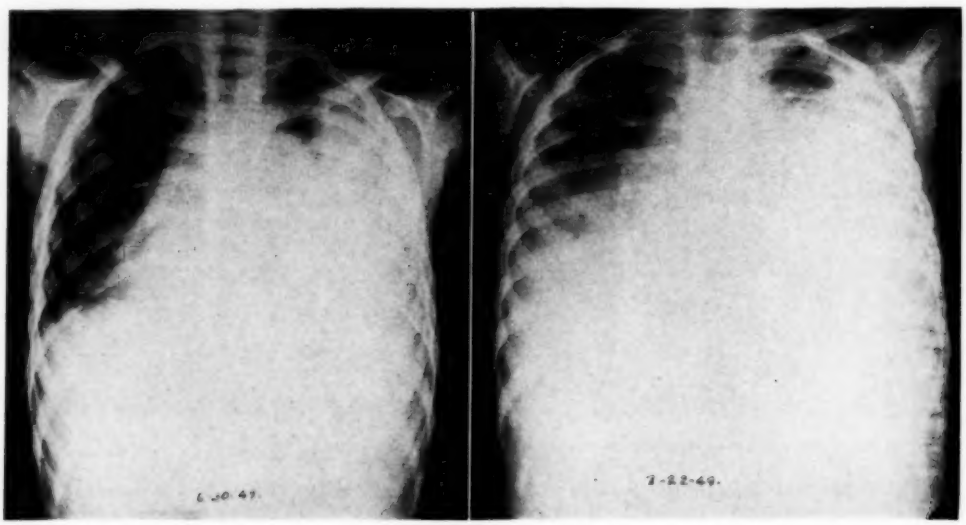

Fig. 4. Fig. 5.

Fig. 4.—Roentgenogram of chest on first postoperative day, showing decrease in size of pericardial outline and appearance of fluid in the left pleural space.

Fig. 5.—Roentgenogram of chest on twenty-third postoperative day showing bilateral pleural effusions.

Thoracenteses, repeated at intervals of several days, produced large quantities of sterile yellow fluid. X-ray examination of the heart after removal of the pleural fluid showed slight cardiac enlargement. The patient showed progressive improvement, the edema and abdominal fluid gradually subsiding. He was sent home on the twelfth hospital day. An electrocardiogram (Fig. 3,*D*) just before dismissal showed changes of improvement and a tendency of reversion to normal.

The patient was seen eight weeks after discharge from the hospital and was asymptomatic. There was no edema nor increased venous pressure. The pericardiotomy scar was well healed. The heart and lungs were normal to physical examination, and the liver was not palpable. X-ray and fluoroscopic examination of the chest (Fig. 6) and the electrocardiogram (Fig. 3,*E*) showed no abnormalities of the heart or lungs. The last observation of the patient was five months later, and the patient appeared healthy in all respects.

DISCUSSION

Pericarditis due to *H. influenzae*, Type B, can be considered a rarity, inasmuch as to date we could find reports of only nine cases in a survey of the available literature (Table I). Six of these cases terminated fatally. All cases were in children under 7 years of age.

Five of these cases appeared in the German literature. Baumeyer,[4] in 1932, reported two cases, both resulting in death. Hotz, in 1939,[5] reported one fatal case. Kleinschmidt,[6] in 1939, reported two cases, one of whom lived. Kresky,[7] at Mount Sinai Hospital, New York, N. Y., reported a fatal case in 1942. In 1947, van der Sar,[8] in the Dutch literature, described a case in which treatment was successful. Two additional patients, one of whom survived, were merely listed among several cases of purulent pericarditis reported by Shipley and Winslow[9] in 1935, and by Adams and Polderman[10] in 1941.

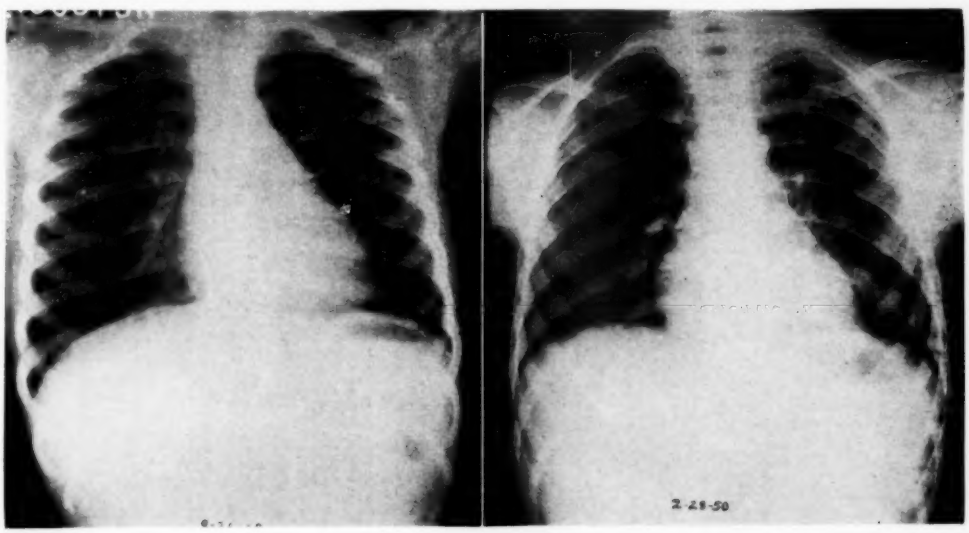

Fig. 6. Fig. 7.

Fig. 6.—Roentgenogram of chest eight weeks after final dismissal from hospital showing complete disappearance of pleural fluid and normal heart outline.
Fig. 7.—Roentgenogram of chest seven months after final dismissal from hospital. Heart and lungs are negative.

Most of the above authors report a constant association of *H. influenzae* pericarditis with a preceding inspiratory stridor, presumably due to influenzal laryngitis. This feature was not noted in our patient.

The diagnosis of purulent pericarditis, whether due to *H. influenzae* or to other organisms, is frequently delayed or overlooked entirely, usually because the condition is obscured by concomitant infectious processes in the chest or other parts of the body. Every patient suffering from an infection with one of the pus-forming organisms should be watched carefully for the development of purulent pericarditis, *despite* the administration of antibiotics.

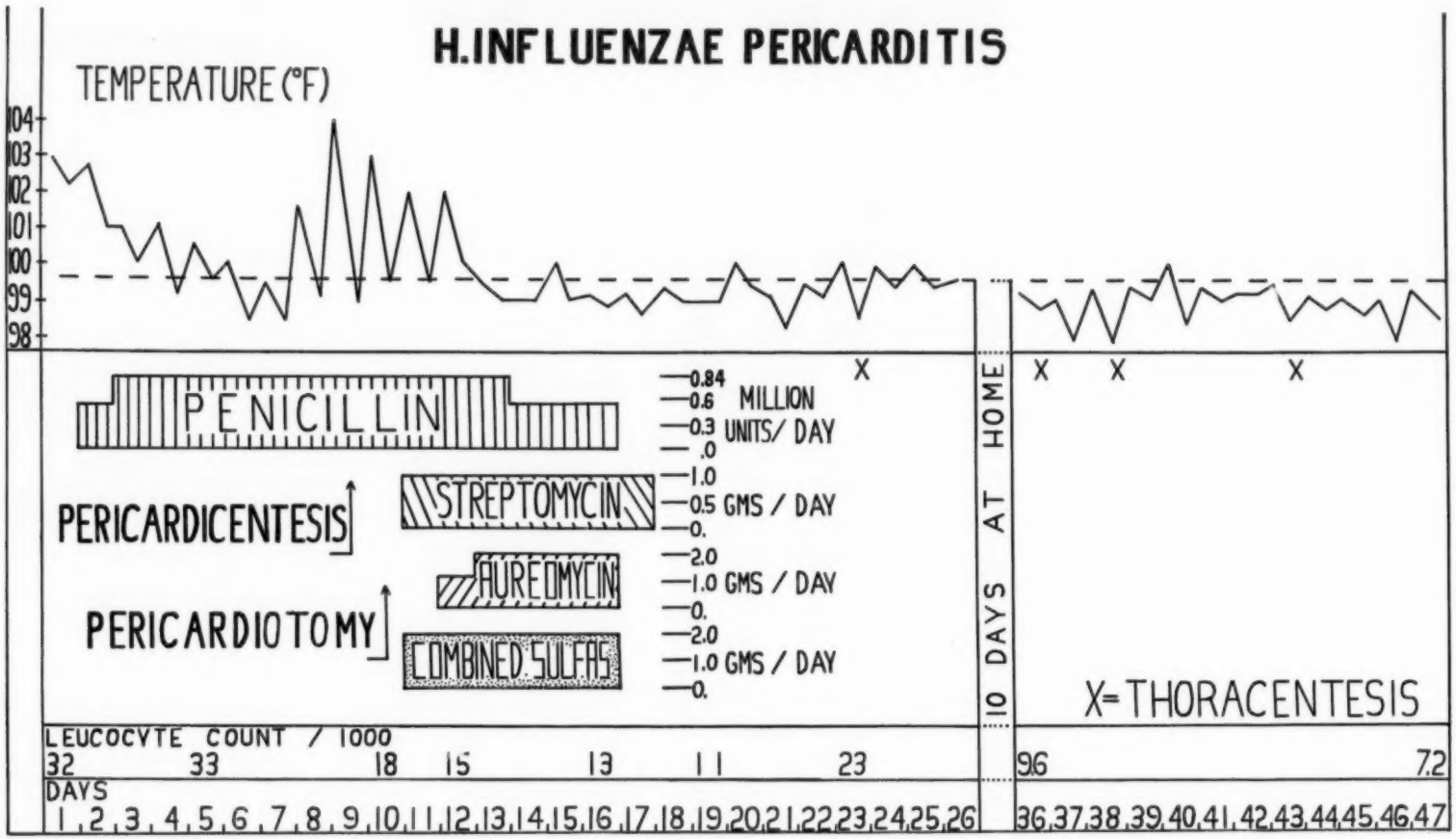

Fig. 8.—Graphic representation of course of patient's illness.

The treatment of purulent pericarditis today includes surgical drainage of the pericardium plus the use of the antibiotics *specific* for the offending organism. Several reports in the recent literature seem to consider the treatment of suppurative pericarditis with repeated pericardial aspirations and instillation of penicillin in conjunction with systemic chemotherapy to be sufficient.[11-19] The superiority of this method to pericardiotomy is not established.[20] Pericardial paracentesis is a procedure fraught with some danger of puncturing the myocardium or lacerating the internal mammary or coronary vessels, whereas exposure of the pericardium under direct vision is a safe procedure obviating these possibilities. There are numerous techniques of performing the surgical drainage of the pericardium, each with its own adherent.[21,22,23]

TABLE I. PREVIOUSLY REPORTED CASES OF HEMOPHILUS INFLUENZAE PERICARDITIS

CASE NO.	AUTHOR	SEX	AGE	TREATMENT	OUTCOME
1	Baumeyer, 1932	Male	4 yr.		Died, fourth day
2	Baumeyer, 1932	Female	2 yr.	Pericardial paracenteses	Died, thirteenth day
3	Shipley and Winslow, 1935	?		Pericardiotomy	Died
4	Kleinschmidt, 1939	Male	3 yr.	Pericardial paracentesis	Died, fourteenth day
5	Kleinschmidt, 1939	Male	6½ yr.	Pericardial paracentesis	Recovered
6	Hotz, 1939	Male	7 yr.	Pericardiotomy	Died, twelfth day
7	Adams and Polderman, 1941	Female	2 yr.	Pericardiotomy	Recovered
8	Kresky, 1942	Female	3 yr.		Died, fourth day
9	Van der Sar, 1947	Female	4 yr.	Pericardiotomy; sulfonamides	Recovered

The patient herein reported fortunately made a complete recovery after surgical drainage and combined antibiotic therapy, in spite of the fact that the patient was treated for several days ineffectively with penicillin alone. Recovery might well have been more prompt if more specific therapy had been instituted sooner. Unfortunately, no in vitro studies were done to determine the sensitivity of the organism to the sulfonamides, penicillin, streptomycin, or aureomycin.

The sulfonamides and streptomycin frequently have been reported as effective in *H. influenzae* infections, and recent reports indicate that aureomycin is equally effective.[24-29] Penicillin has not been shown to be of significant benefit in most cases. It is difficult to determine which of the antibiotics employed in this case was the most beneficial. Penicillin apparently had little effect. The favorable response of the patient and the prompt drop of temperature following pericardiotomy and the institution of combined antibiotic therapy suggests that both of these measures may be given credit.

The episode of fluid retention, which developed after the subsidence of the fever, was thought to be due to an actual myocarditis resulting from the infection, rather than to mechanical pressure on the heart or to constriction of the great veins. It was during this stage that the significant electrocardiographic changes

occurred for the first time. With bed rest, removal of chest fluid, and general supportive therapy, evidence of cardiac failure subsided and the electrocardiographic abnormalities disappeared.

Any opinion as to the patient's chances of developing chronic constrictive pericarditis in the future would be purely speculative. A number of these cases are thought to be due to tuberculosis, but a small percentage follow suppurative pericardial infections. Shipley and Winslow,[31] in a follow-up of twenty-nine cases of purulent pericarditis five months to twenty-one years after pericardiotomy, reported that twenty-five patients were living and well. Two patients developed adhesive pericarditis, and one died. It is suggested by Levine[32] that in the future more cases of chronic constrictive pericarditis will be seen on the basis of previous septic pericarditis in patients who survive the acute illness with the aid of antibiotics.

SUMMARY

1. A case of purulent pericarditis caused by *H. influenzae*, Type B, with recovery following pericardiotomy and antibiotic therapy is reported.

2. The importance of early diagnosis and treatment of purulent pericarditis is emphasized.

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SCLERODERMA HEART DISEASE

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SCLERODERMA as it affects the skin has been well known for years but only recently has it been recognized as a diffuse disease of collagenous tissue. Skin changes, metastatic calcification, muscle and gastrointestinal tract lesions are well known. Weiss, Stead, Warren, and Bailey,[5] in 1943, were the first to call attention to the involvement of the heart in this disease, reporting seven cases with two autopsies. Other case reports of scleroderma with myocardial involvement since 1943 are those of Goetz,[2] East and Oram,[1] Mathison and Palmer,[3] and Spain and Thomas.[4] In two of these, death was attributable to the myocardial lesion. The purpose of this paper is to report another case of scleroderma with heart failure and to discuss briefly the cardiac manifestations of scleroderma.

CASE REPORT

First admission, Nov. 18, 1947: This 51-year-old mechanic had been well until about six weeks before admission when he developed severe shoulder pain radiating to both hands. A daily temperature elevation was not altered by penicillin. Three days before admission the right arm became swollen and discolored, and there was pain and tenderness in the swollen area. He had lost 15 pounds in the six weeks before admission.

On physical examination he was seen to be a well-developed, febrile white man. Marked soft tissue swelling, slight tenderness, and superficial venous distention were noted over the right chest and arm. The right superficial jugular vein was distended. The blood pressure was 120/64 mm. Hg, the pulse 100, and the temperature 101° F. No other significant physical findings were noted.

The white blood cell count on admission was 17,000 with a differential of 90 per cent neutrophils, 4 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils. The hemoglobin was 11.7 Gm. and the sedimentation rate 40 mm. per hour. The urine had a specific gravity of 1.023 and showed 3 plus albumin and 2 to 20 white blood cells per high power field. The blood Kahn was negative. A chest film showed an area of density in the right lower lung field.

The hospital course was characterized by persistence of fever with daily elevations to 101° F. Leucocytosis ranging from 11,000 to 19,000 persisted for two and one-half months. Later, with counts of 8,000 to 10,000 a 6 per cent eosinophilia was noted on several occasions. Albuminuria (1 to 2 plus) persisted, and Bence-Jones protein was found repeatedly. The blood urea nitrogen was 10 mg. per cent. An intravenous pyelogram demonstrated a small calculus in the right middle calyx. *Aerobacter aerogenes* was cultured from the urine. The serum albumin was 2.7 Gm. and

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the globulin 3.5 Gm. per cent. Blood cultures were negative. The bone marrow showed myeloid and moderate erythroid hyperplasia. Two muscle biopsies showed normal myocytes, blood vessels, and connective tissue. An electrocardiogram was normal. The density in the right lung gradually resolved and was interpreted as an infarct. The venous distention and soft tissue swelling were believed due to thrombosis of the right innominate vein.

On Jan. 15, 1948, the right dorsalis pedis artery suddenly became occluded. The temperature of the foot returned to normal in about two weeks, but pulsations could no longer be felt in this artery. The shoulder pain persisted for three months. Physical therapy and manipulation under anesthesia improved motion of the joint. The urinary tract infection did not respond to treatment with mandelic acid, streptomycin, penicillin, and sulfonamides. The daily temperature elevations persisted until early May, 1948, with peaks of 100° F., but thereafter remained normal. The albuminuria and Bence-Jones proteinuria disappeared. The sedimentation rate remained near 40 mm. per hour. The patient was discharged May 28, 1948, with no definite diagnosis established.

On examination on two recall admissions in August and November, 1948, he complained of residual stiffness of the left shoulder and numbness of the right foot. For the first time he complained of stiffness of the fingers, and these were described as showing arthritic changes. He had regained 25 pounds in these six months and had returned to work. The temperature was normal, the blood pressure 120/70 mm. Hg, and the pulse 80. The sedimentation rate was 54 mm. per hour. The urine contained a trace of albumin and 10 to 15 white blood cells per high power field.

Fourth admission, March 11, 1949: In February, 1949, the patient developed "erysipelas" of the eyelids, face, and ears, and generalized pruritus. Treatment by his local physician with sulfonamides gave temporary improvement, but this was followed in two weeks by anorexia, nausea, and recrudescence of pain in the knees and left hand. Overnight his legs became too weak to support him. He complained of numbness and of a prickling sensation on pressure in the lower extremities for which he again sought admission.

On physical examination he appeared chronically ill. A red, scaling dermatitis involved the face and ears while an ill-defined, red, lichenified dermatitis was present on the back with discrete, sharply defined patches on the anterior left shoulder and on the knuckles. Atrophic shiny skin of the fingers was noted. A history of Raynaud's phenomenon could not be obtained. The blood pressure was 128/84 mm. Hg, the pulse 100. No murmurs were heard and the heart was not enlarged. The left shoulder was ankylosed, and motion of the right shoulder was impaired. There was weakness in both arms, shoulder girdles, legs, and thighs, including the gluteals. Reflexes were absent in the lower extremities and diminished in the arms. Vibration sense was diminished, and slight loss of temperature and superficial pain sense was described for the lower extremities and hands. Deep pain was unimpaired. Coordination and the cranial nerves were normal. The axillary lymph nodes were slightly enlarged.

The white blood cell count was 16,000 with 70 per cent neutrophils, 26 per cent lymphocytes, and 4 per cent eosinophils. The hemoglobin was 13.7 Gm. Subsequent white blood cell counts varied from 9,000 to 21,000 with an 8 per cent eosinophilia recorded on one occasion. The sedimentation rate was 26 mm. per hour. The urine had a specific gravity of 1.026 and showed a trace of albumin and 10 to 15 white blood cells per high power field. Urine cultures grew *A. aerogenes*. The spinal fluid on admission showed 44 red blood cells per cubic millimeter. The total protein was 250 mg. per cent. The colloidal gold curve was 3444222110; the Wassermann was negative. Ten days later, the spinal fluid contained 1 white cell per cubic millimeter and the protein was 140 mg. per cent. The serum albumin was 3.2 and the globulin 3.3 Gm. per cent. Biopsy of the skin of a finger showed changes consistent with a diagnosis of scleroderma. A chest roentgenogram was normal. An esophagram was normal, and roentgenograms of the fingers showed radiopacities in the soft tissue of the most distal portions of the fingers of the right hand. The urinary tract infection persisted. Electrocardiograms were normal.

The patient was afebrile throughout his hospital stay. Three months after admission he had regained use of the legs, and the involved skin areas of the face and trunk now showed brownish pigmentation and were thin and smooth. The hands remained unchanged with inelastic, thin, tightly adherent, unwrinkled skin (Fig. 1). A spinal fluid examination was now normal. De-

creased vibration and position sense persisted, but reflexes of the lower extremities returned. He was discharged Aug. 5, 1949, six months after admission, with a diagnosis of scleroderma.

Fifth admission, Nov. 1, 1949: The patient had been well except for stiffness in the knees and fingers until two weeks before admission when he caught a cold. Eight days before admission he first noted marked exertional dyspnea, and that evening the ankles were swollen. He became orthopneic. There were no gastrointestinal complaints other than vomiting which started the day before admission.

Fig. 1.—Photograph of the hands in April, 1949. The skin of the distal portions of the fingers is tight, thin, and unwrinkled.

Physical examination revealed a severely ill, orthopneic white man with marked cyanosis of the face, hands, and feet. The neck veins were markedly distended. The blood pressure was 126/90 mm. Hg, the pulse 120 and regular. A Grade 2 apical systolic murmur and a protodiastolic gallop were heard. The respiratory rate was 34 per minute. There was dullness with absent breath sounds over both lung bases. No râles were heard. The liver was percussed 2 finger-breadths below the costal margin, and there was tenderness in this region. Pitting edema involved the sacrum and abdominal wall and was massive in the legs and scrotum. The patient was digitalized, given morphine, mercurials, and oxygen. This therapy combined with bilateral thoracentesis, at which 600 c.c. of fluid were removed on two occasions, resulted in improvement for about ten days. He lost 20 pounds rapidly but continued to be dyspneic and cyanotic. The blood pressure fell to 98/68 mm. Hg. The heart tones were now distant, and no murmur could be heard. The gallop rhythm persisted. A thrombophlebitis developed in the veins of the right arm. A left pleural friction rub was heard and persisted until death.

Chest roentgenograms showed pulmonary congestion, bilateral pleural effusion, and a slightly enlarged heart. The white blood count was 17,000 with 92 per cent neutrophils and 8 per cent lymphocytes. The hemoglobin was 9.3 Gm., the sedimentation rate 106 mm. per hour. The specific gravity of the urine was 1.013. It contained 4 plus albumin and 5 to 10 white blood cells per high power field. Electrocardiograms (Fig. 2) showed marked change from previous

admissions with very low voltage in the limb leads, first-degree heart block, low precordial R waves through Lead IV, and low precordial T waves. Subsequent tracings showed further increase in the P-R interval, disappearance of the precordial R waves through Lead IV, and depression of $ST_{5,6}$. Numerous ventricular premature beats appeared and digitoxin was discontinued. He continued to fail and died on Nov. 29, 1949.

In brief summary, this 51-year-old mechanic had a prolonged illness with an acute febrile onset followed by arthralgia, anemia, arterial and venous thromboses, and muscle weakness and atrophy. Later, he developed skin changes of the face, trunk, and hands with x-ray evidence of

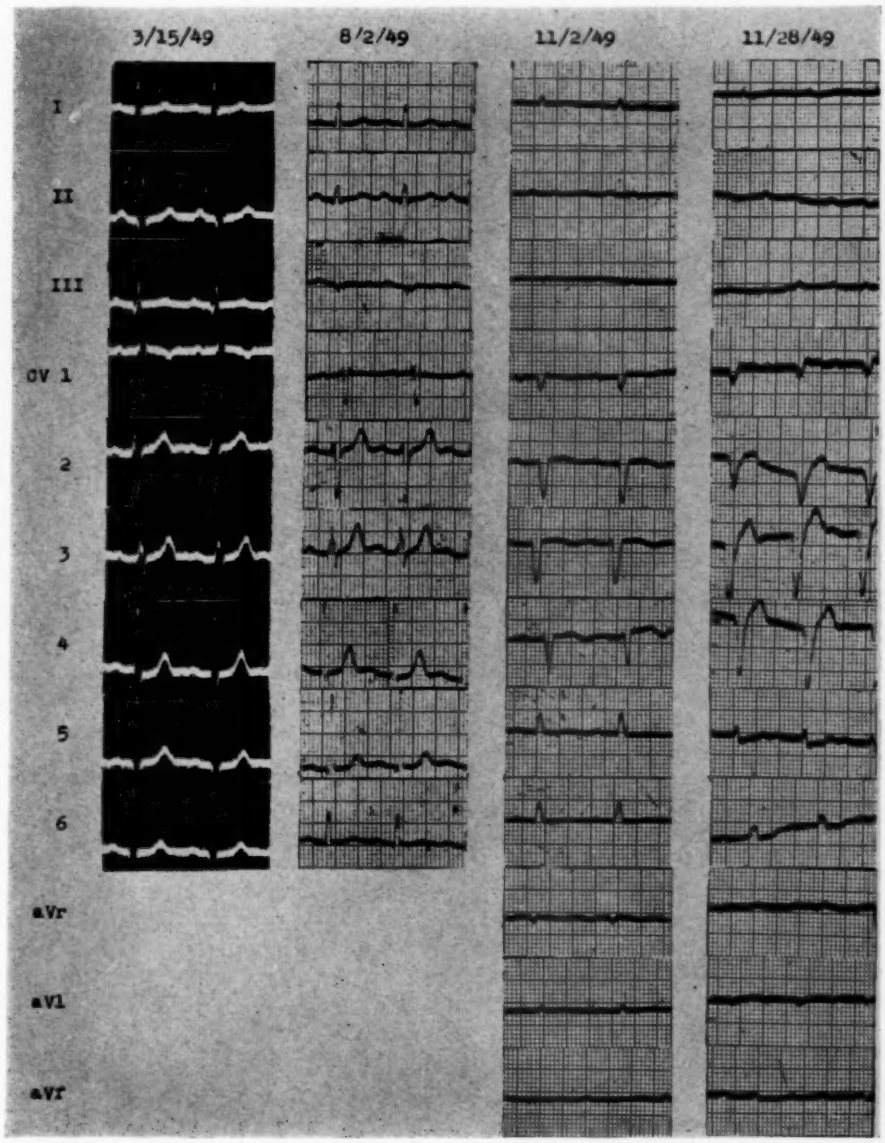

Fig. 2.—In these representative electrocardiograms there is a progressive decrease in the amplitude of the QRS complexes in the limb leads. The P-R interval is prolonged in the tracings of Nov. 2, 1949, and Nov. 28, 1949. The R waves are absent in Leads CV_{1-4} in the tracing of Nov. 28, 1949.

finger-tip calcification. Death occurred five weeks after the first symptoms of heart failure and two years after the onset of the illness. A urinary tract infection persisted throughout the illness.

Autopsy.—The autopsy was conducted three hours after death. The body was of average size and normal development but revealed evidence of recent weight loss. Edema of the sacrum and lower extremities was prominent. The skin of the back, face, ears, hands, and shoulders revealed atrophic changes. Over the back, particularly on the left, this was accompanied by a diffuse brownish pigmentation. Gross atrophy of the muscles of the shoulder was present on the left. The skin of the fingers was immobile, and two small ulcers were present at the nail base of the third and fourth fingers on the right hand. The nail of the fourth finger was soft and draining.

The abdominal cavity contained no excess fluid; the organs appeared normal in situ. The left pleural cavity contained 500 c.c. of clear, yellowish-brown fluid and fibrous adhesions around the upper lobe; the right pleural cavity contained 1,000 c.c. of a similar fluid. The pericardial cavity contained over 100 c.c. of clear amber fluid.

The heart weighed 450 grams. The epicardium, all four valves, the valve rings, and the ventricular endocardium appeared normal. The right auricle contained an organized thrombus, and the interatrial septum on the right revealed two small, white endocardial scars. The myocardium in general felt soft and flabby. The left ventricular myocardium revealed a diffuse fibrosis and was thinned to 5 mm. in the anterior wall near the apex. The fibrosis appeared to be primarily subepicardial and only rarely, as in the thinned area, appeared to involve the entire myocardium. The interventricular septum revealed a similar diffuse fibrosis. The right ventricle seemed normal on gross inspection. The coronary ostia were normally situated and widely patent. The coronary arteries were of normal size, ran a normal anatomical course, and revealed a slight to moderate intimal atherosclerosis. The lumina were always widely patent, and no occlusion by either sclerosis or thrombosis was demonstrable. The aorta and large arteries revealed moderate intimal atherosclerosis. A few small, atheromatous plaques were found in the main pulmonary artery. The superior and inferior venae cavae were normal. A small sessile thrombus was found in the right common iliac vein.

The left lung weighed 550 grams, the right 475 grams. The bronchi of both lungs were filled with tenacious blood-tinged, mucoid material, and both lungs were partially atelectatic. On cut section four small areas of infarction were noted, three in the left lung and one in the right lower lobe. Gross thrombi in the smaller pulmonary arteries supplying the infarcted areas were easily demonstrated.

The liver weighed 1,500 grams and on section presented a nutmeg appearance. The spleen weighed 175 grams and revealed patchy areas of hyaline thickening of the capsule. On section the pulp was dark red and firm with inconspicuous Malpighian corpuscles.

The esophagus appeared normal grossly without evidence of thickening or ulceration. The stomach, duodenum, and jejunum revealed no abnormality. Starting at the ileum, the remainder of the gastrointestinal tract was filled with dark red fluid blood and clots. When washed away, there remained areas of diffuse submucosal hemorrhage with a segmental distribution. The portions of bowel between the hemorrhagic areas appeared normal. No ulcerations were demonstrable with the naked eye. The mesenteric vessels, as far as they could be followed, were free of occlusion.

On examination the pancreas, adrenals, urinary tract, genital organs, lymphatic system, organs of the neck, bones, brain, spinal cord, and peripheral nerves all appeared normal.

Microscopic Examination.—All tissues were examined histologically with hematoxylin and eosin stain. A number of the tissues were also stained with azocarmine.

The skin from areas showing atrophic changes grossly also revealed marked atrophy of the epidermis and skin appendages. The epidermis was thin, the rete pegs blunt, short, and reduced in number. There was a definite increase in the melanin pigment of the basilar layers. The corium was composed of dense acellular broad bands of collagen. The venous plexus of the upper corium was prominent in some sections and showed a mild perivascular lymphocytic infiltration. The sebaceous and apocrine glands were compressed and degenerating.

Muscle from the area of atrophy in the left deltoid revealed atrophic changes. Individual myocytes were shrunken, pale staining, and separated from their sarcolemmal sheath to produce a vacuolated appearance. Striations were indistinct or absent in these fibers. A minimal proliferation of the collagenous connective tissue was noticed between the muscle fibers. Inflammatory changes were scant, consisting in scattered small foci of lymphocytic infiltration.

Sections of the myocardium revealed a consistent pathologic process in all parts of the auricles and ventricles (Fig. 3). There was a marked overgrowth of connective tissue which extended into the epicardium in many areas. This fibrosis was not limited to the perivascular spaces but was diffuse. It frequently presented a prominent vascularity somewhat resembling granulation tissue. Accompanying this was some degree of destruction of the muscle parenchyma. In a few places the muscle appeared entirely destroyed and replaced by fibrous tissue. In most areas

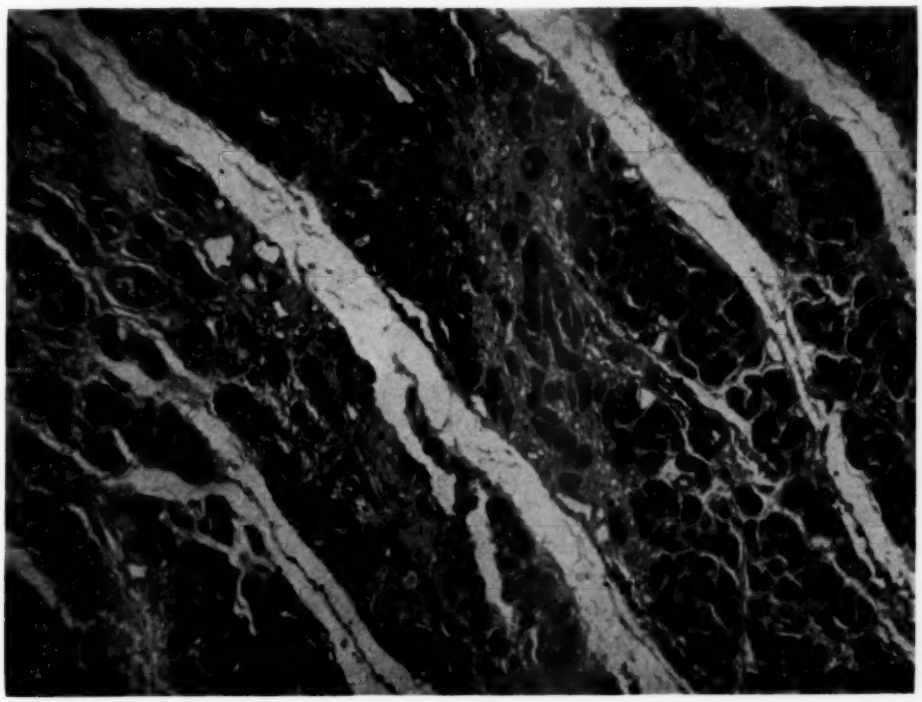

Fig. 3.—There is an extensive fibrosis of the left ventricle. This fibrous tissue contains numerous blood vessels. The small arteries and arterioles show some hyaline thickening, but their lumina are patent. Leucocytic infiltration is slight, and atrophic change in the myocytes is minimal even where the muscle fiber is completely surrounded by fibrous tissue.

the fibrosis surrounded individual myocytes or groups of muscle fibers. Some of these fibers appeared histologically intact, but many revealed degenerative changes with varying degrees of fragmentation, loss of striations, and/or karyolysis of the nuclei. No frankly necrotic areas of muscle were found. Cellular infiltration was most marked in the areas showing the most fibrosis but was never prominent. It consisted of lymphocytes, plasma cells, and macrophages, some of which contained fine yellowish pigment. No Aschoff bodies, tubercles, or other specific myocarditis were evident in any of the material examined. The small intramural arteries revealed hyaline thickening of their walls, but attenuation of the lumen was minimal and of insufficient degree to account for the extensive fibrosis.

The lungs revealed necrosis of the tissue in the areas of infarction. There was thickening of the interalveolar septa adjacent to the areas of infarction with epithelization of many of the

alveoli. In a few areas proliferating fibrous tissue replaced the pulmonary parenchyma. Cellular infiltration was minimal and consisted primarily of macrophages, a number of which contained coarse, granular yellow pigment.

Sections of the esophagus taken from the middle one-third showed marked fibrosis of the wall. Dense collagenous connective tissue replaced the normal components of the esophagus from submucosa through the entire musculature. At the edge of the areas of fibrosis there was active proliferation of the fibroblasts, and the muscle fibers showed degenerative changes. The mucous membrane was thin and infiltrated by mononuclear cells. One small area of ulceration was seen, surrounded by an acute inflammatory process. In the area of fibrosis and inflammation the small vessels showed thickening of the intima and media, and in the area of ulceration many of these small vessels were occluded by thrombi. The ileum revealed multiple hemorrhagic superficial ulcerations of very small size surrounded by an acute inflammatory reaction and showing thrombosis of the small vessels in the area of inflammation. There was rather marked edema of the submucosa adjoining the areas of ulceration but no marked increase in the fibrous tissue such as was found in the esophagus. The small vessels of the bowel showed a hyaline thickening of their walls but no obstruction to the lumen was found except in the areas of ulceration.

The liver revealed evidence of chronic passive congestion with atrophy of the central portion of the lobules and yellowish pigmentation of the atrophic cells. Sections of the other visceral organs were all normal.

Sections of the brain revealed only minimal degenerative changes resulting from cerebral arteriosclerosis.

There was no increase in the connective tissue of the peripheral nerves, although rather marked sclerotic process in the small arteries and arterioles consisting of an intimal proliferation and medial fibrosis was seen. No occlusion of the vessels could be demonstrated.

TABLE I

	AGE	SEX	PERIPHERAL EDEMA	ORTHOPNEA	GALLOP RHYTHM	BLOOD PRESSURE	DURATION OF CARDIAC SYMPTOMS	HEART WEIGHT (GRAMS)	NORMAL CARDIAC VALVES AND PATENT CORONARY ARTERIES
Case 1 Weiss and associates	27	F	Yes	Yes	Yes	140/100	12 mo.	300	Yes
Case 2 Weiss and associates	56	F	Yes	No	Yes	160/110	9 mo.	500	Yes
Case 3 East and Oram	49	M	Yes		Yes	120/78	12 mo.	370	Yes
Case 4 Mathison and Palmer	23	F			Yes	106/75	24 mo.	290	Yes
Case 5 Goetz	44	F	0	Yes		100/65	About 2 yr.	226	Yes
Case 6 Hurly, Coe, and Weber	51	M	Yes	Yes	Yes	126/90 98/68	5 wk.	450	Yes

COMMENT

A case of scleroderma with death from heart failure has been described. The skin, visceral, and myocardial changes were those described in other cases of scleroderma.

Table I lists some of the prominent clinical and pathologic findings in the other cases of scleroderma heart disease with reported autopsies. Peripheral edema, orthopnea, enlarged liver, enlarged heart shadow, and a gallop rhythm were common findings. The duration of cardiac symptoms varied from five weeks to two years. Hypertension was present in two patients, and two complained of mild precordial pain relieved by rest.[1,3] In one case cardiac symptoms preceded scleroderma by several months.[5]

Weiss and associates described a triangular heart shadow with widening of the supracardiac area. This was not found in the other reports nor in our case. The described electrocardiographic changes were not specific. They consisted of low voltage in the limb leads, premature beats of either auricular or ventricular origin, and varying degrees of heart block. Complete heart block was present in one case.[1] The laboratory findings were not characteristic.

In the reported cases, gross changes in the hearts were not striking. The heart may show visible linear markings or tiny gray or translucent areas of fibrosis within the myocardium. The microscopic changes in scleroderma heart disease consist in the loss of muscle tissue and a patchy infiltration by a peculiar connective tissue which in many areas is very rich in capillaries and resembles granulation tissue. The fibers of this connective tissue are not thickened and do not show fibrinoid degeneration. In contrast to lesions due to vascular disease, islands of muscle are not found primarily around arteries. Absence of inflammatory reaction is noteworthy. Degenerative changes may be seen in some muscle fibers.

SUMMARY

1. A case of scleroderma heart disease, a rare cause of heart failure, has been described.

2. A brief review of the cardiac pathology has been presented.

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LOWER NEPHRON NEPHROSIS ASSOCIATED WITH PROLONGED SHOCK FROM VENTRICULAR TACHYCARDIA

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DURING the past ten years interesting data have been accumulated on an affection of the kidney usually associated with clinical states characterized by "shock." Because of the localization of the pathologic lesion to the distal portion of the renal tubules, Luckè[2] applied the term "lower nephron nephrosis" in 1946. This term has gained considerable popularity and is understood to include "crush snydrome," "hemoglobinuric nephrosis," and other closely related conditions. The etiology of the tubular lesions is incompletely understood. Van Slyke and others believe that the most important factor is renal ischemia.[1-3] However, other plausible explanations have been suggested[4-6] and a multiplicity of allied causes probably exists. Since World War II, when the condition was found to be common following trauma, many reports have appeared describing the syndrome in a number of other clinical situations. Shock associated with ventricular tachycardia is commonly encountered in clinical medicine, but this renal condition has been rarely reported as a sequel.

CASE REPORT

The patient, J. O., was a 46-year-old, retired, white man, a professional soldier who was well until he suffered a myocardial infarction while in the Army in April, 1949. He made an uneventful recovery and was discharged for coronary artery disease. He was first seen at Kennedy Veterans Administration Hospital in April, 1950, complaining of vague, anterior chest pain of a dull, aching character, not related to exertion. Electrocardiograms showed a stable pattern consistent with right bundle branch block and remote anteroseptal infarction.[7] Routine urinalysis was normal with a specific gravity of 1.022. The blood pressure was 110/70 mm. Hg. He was discharged after ten days of hospitalization, the final impression being that his present symptoms were largely due to anxiety and introspection, although his coronary artery disease was fully appreciated. He returned to the hospital in July, 1950, because of three or four brief episodes of syncope, not associated with convulsions or conscious disturbance of the cardiac rhythm. Examinations at that time showed a borderline electroencephalogram. The diagnosis rested between epilepsy and Stokes-Adams seizures. No attacks occurred during hospitalization, and a definite diagnosis was not made.

For several days preceding the last admission on Aug. 30, 1950, the patient experienced dull, retrosternal aching more frequently than usual. While transacting business in a bank about 10 A. M. on the day of admission, he suddenly lost consciousness for five or six minutes. A doctor was summoned who gave him a hypodermic injection and sent him by ambulance to the hospital 120 miles away.

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On admission the patient was fully conscious and complaining of mild retrosternal aching. The skin was warm and dry. Blood pressure was 90/70 mm. Hg. The apical heart rate was 250 per minute (patient was not conscious of tachycardia). There was no congestion of the lungs, hepatic enlargement, nor dependent edema. Electrocardiograms, including esophageal leads, showed a ventricular tachycardia with a ventricular rate of 240 per minute and an auricular rate of 140 per minute. Patient was put in an oxygen tent and given morphine, ¼ gr. Quinidine,

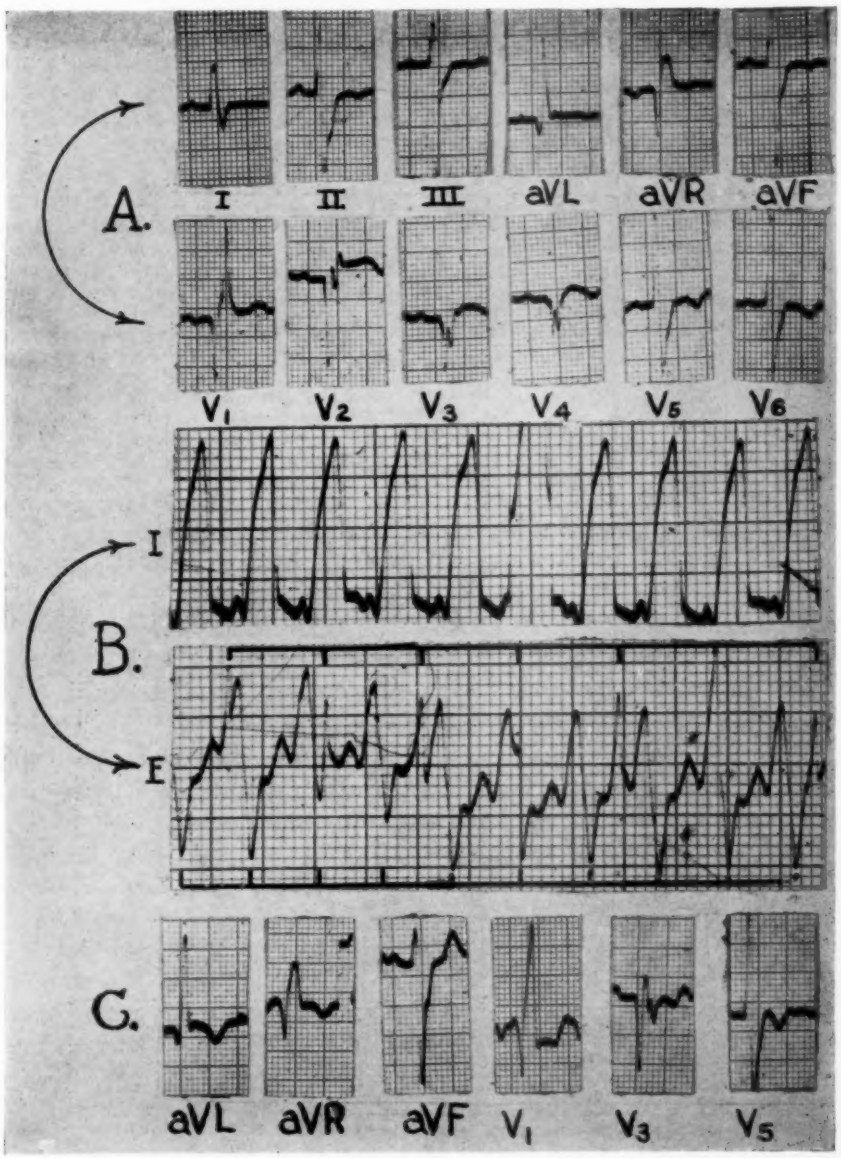

Fig. 1.—*A*, Tracing taken six weeks prior to last admission. *B*, Lead I and esophageal leads show ventricular tachycardia. The ventricular rate was 240, auricular rate 145. P-wave peaks are designated in the graph at the top of the tracing, QRS complexes at the bottom. *C*, Tracing taken several days after cessation of the tachycardia.

9 gr., was given by mouth, followed in an hour by another dose of 6 gr. The tachycardia persisted and the patient became ashen and apathetic and sweated profusely. The blood pressure fell to 80/70 mm. Hg. At the end of the second hour the patient began to vomit, and oral medication was impossible for the next thirty-six hours. Fifteen hundred c.c. of plasma and 30 mg. of Neo-Synephrine Hydrochloride were given intravenously during the next twelve hours to combat the shock, but a systolic blood pressure above 80 mm. Hg could not be maintained. Quinine dihydrochloride, 30 gr., was given intravenously over a two-hour period in a vain attempt to stop the ventricular tachycardia. Atropine, 1/50 gr., was also unsuccessful.

TABLE I. CLINICAL COURSE

HOSPITAL DAY	INTAKE (C.C.)	OUTPUT (C.C.)	NONPROTEIN NITROGEN (MG. %)	BLOOD CHLORIDES (MG. %)	REMARKS
1	Not recorded	0			Tachycardia; severe shock; severe vomiting; 1,500 c.c. plasma, Neo-Synephrine Hydrochloride, quinine, atropine
2	2000	50	47	480	Tachycardia stopped with I.V. quinidine; out of shock; still vomiting; parenteral glucose and saline solution; urine specific gravity 1.020 with trace of albumin; CO_2 59 vol. per cent
3	2500	0 ?		400	ECG unchanged from tracings 5 months previously; 1,000 c.c. N. saline solution; regular liquid diet
4	2500	375	68	380	Regular liquid diet; less nauseated; urine specific gravity 1.008; trace of albumin
5	3180	650			ECG stable; hiccup; retaining oral feedings well
6	3690	1100			Hiccup; regular diet
7	3300	2600	114	400	Serum potassium 19 mg. per cent; lungs mildly congested; hiccup; soft diet (no sodium restriction); blood pressure 150/90 mm. Hg
8	2540	2700	132	360	Hiccup; urine pale; specific gravity 1.009; blood pressure 160/102 mm. Hg; confused and apprehensive
9	4180	3250	128	340	Hiccup; low protein diet; slightly confused
10	4060	4460	132		Hiccup; slightly confused
11	3480	2940	133		No hiccup; serum potassium 16 mg. per cent; eating well
12	3600	2100			Sensorium clearer
13	3570	2810	88	400	Improving steadily
14	2790	2600			
15	2360	2100	61		
16	2160	2050	64		Improving steadily
17	2580	1950	50		
18	2580	950			
19	2520	1250	31		
20	2700	1230			Appeared fully recovered; still at bed rest

Urea clearance was 71 per cent on the twenty-fourth day. Concentrated urine to specific gravity of 1.017 on the thirty-eighth day.

About 11 o'clock the next morning, the patient having been in shock for approximately fourteen hours, parenteral quinidine* was obtained, and the patient was given 9 gr. intravenously over a period of about ten minutes. Continuous electrocardiographic tracings were taken. The ventricular tachycardia ceased, and the heart reverted to a sinus rhythm showing a second-

*Injectable quinidine hydrochloride, Brewer and Company, Inc., Worcester, Mass.

degree atrioventricular block for about an hour. Within one-half hour the blood pressure rose to 100/80 mm. Hg, and the patient's general condition improved dramatically. He voided, for the first time, 50 c.c. of dark urine. Because of the severe vomiting, a liter of glucose in normal saline solution and a liter in distilled water were given by hypodermoclysis.

During the next several days the blood pressure gradually rose to a high of 160/102 mm. Hg, and the nausea gradually subsided but marked oliguria was observed. The urine was pale with a specific gravity always near 1.010. A trace of albumin was reported in most specimens. The urine was not examined for iron-containing pigments. The nonprotein nitrogen, which was normal on admission, rose to 133 mg. per cent. Liberal fluid intake without sodium restriction was given. About the end of the fifth hospital day, it was fully appreciated that a lower nephron nephrosis had occurred. At this time the patient was dull, slightly confused, and had developed a persistently recurring hiccup. Moderate pulmonary congestion occurred but no peripheral edema. A diuresis began on the seventh hospital day. The nonprotein nitrogen reached a peak of 68 mg. per cent on the eleventh day and gradually returned to a normal of 31 mg. per cent on the nineteenth hospital day. Electrocardiograms showed a reversion to the previous pattern of right bundle branch block and anteroseptal infarction except for minor ST-T changes. An extension of this infarct was suspected but not definitely proved. The patient showed no further disturbance of cardiac rhythm and gradually became ambulatory after four weeks of bed rest. Urea clearance on the twenty-fourth hospital day was 71 per cent of the average normal (calculated on the basis of the maximum clearance formula). A concentration test done on the thirty-eighth hospital day showed a maximum specific gravity of 1.017. The patient was eventually discharged after forty-two days of hospitalization, ambulatory and in relatively good condition.

DISCUSSION

This case presented several interesting problems. First, the episodes of syncope were most likely due to an abrupt fall in the cardiac output from ventricular tachycardia. It is noteworthy that the patient was not conscious of any alteration in the beating of his heart even at a rate of 240 per minute.

Because of the intraventricular conduction defect, the diagnosis of ventricular tachycardia on routine electrocardiographic leads was uncertain. Esophageal leads showed clearly that the auricular rate was about 140 per minute and left no doubt as to the nature of the tachycardia. This, of course, was most important in the treatment. Intravenous quinidine in this case appeared to be life saving.*

The first evidence of azotemia and oliguria was discounted because of extrarenal factors that could have produced it. However, the persistence of the azotemia, even while the renal output was above 3,000 c.c. per day for several days, and the pale urine of low fixed specific gravity were indicative of a more profound derangement in the kidney. The hypertension, hypochloremia, and diuresis on the seventh and eighth days are all in keeping with the clinical course of lower nephron nephrosis. Fortunately, the condition was relatively mild, and the patient was able to tolerate a liberal fluid intake without overloading the damaged circulatory system. The mechanism would appear to be due to renal ischemia since he received no blood, sulfonamides, or other medications implicated in the etiology of this condition. Copious vomiting, pointed out by Lucké[2] as commonly associated with this disorder, was present. After recovery, test doses of quinidine and quinine were given and no untoward effect was observed.

*The intravenous use of quinidine is hazardous. It should only be given with the utmost caution and only after the calculated risks have been balanced in its favor.

SUMMARY AND CONCLUSIONS

1. A case of lower nephron nephrosis following profound shock from ventricular tachycardia is presented.

2. The value of esophageal leads in demonstrating the exact mechanism of abnormal cardiac rhythms is demonstrated.

3. When oral medication is not possible, parenteral quinidine for ventricular tachycardia may be life saving.

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Review of Recent Advances

THE PRESENT STATUS OF THERAPY OF THE CARDIAC ARRHYTHMIAS WITH QUINIDINE

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I. INTRODUCTION

QUINIDINE has been used with variable enthusiasm for the last thirty years. During this period, various cardiologists have expressed widely different opinions on the indications, dosages, and dangers of the use of quinidine. As expressed by Parkinson and Campbell,[1] "Opinion has passed through three stages—first, of enthusiasm following Frey's observation that quinidine could restore normal rhythm in auricular fibrillation; second, of disappointment when the risk of misadventure and the frequency of relapse in unselected cases became realized; third, of discrimination in the choice of patients where danger may be least and the probable advantage greatest." The variation in opinion has been due largely to two facts: (1) Patients to whom quinidine has been administered have had organic heart disease, and it is well known (see below) that unpredictable accidents occur in these individuals even when quinidine is not used; (2) until recently, no satisfactory method for determination of the level of quinidine in the blood has been available. Therapy in the past, therefore, was often based on an arbitrary rather than on a quantitative and physiologic approach.

It is the purpose of this review to re-examine the subject of quinidine therapy in the light of our own experiences in the past four years, utilizing the knowledge obtained of the relationship of the concentration of quinidine in the blood to the prevention and treatment of the cardiac arrhythmias. Up to July 1, 1951, we have data on the concentration of quinidine in the blood with respect to dosage and toxicity in ninety-three* instances of successful conversion of chronic auricular fibrillation and flutter (119 attempts in 111 patients, or 80 per cent successful conversion), as well as data on fifty patients in whom quinidine was used for the prevention of recurrent acute arrhythmias.[5-9]

Since several reviews of the drugs used in the arrhythmias have appeared recently,[2,3] as well as a new book[4] on quinidine, a complete survey will not be attempted. Instead, emphasis will be placed on (1) the advances that permit

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*This includes fifteen patients studied through the courtesy of Dr. Mervyn J. Goldman, Veterans Hospital, Oakland, and nine studied with Dr. Norman Sweet, San Francisco Hospital.

more effective use of the drug, with discussion of the importance of the concentration of quinidine in the blood and the contribution which knowledge of the concentration has made toward a better understanding of dose-time relationships, methods of administration, and similar problems, (2) an analysis of the so-called contraindications to the use of quinidine and a discussion of its dangers, and (3) newer approaches to the prevention of recurrent arrhythmias and arrhythmias complicating surgical operation, myocardial infarction, and other conditions.

II. THE IMPORTANCE OF BLOOD LEVELS

During the war, Brodie and Udenfriend[5] developed a fluorometric method for determining the concentration of quinine and quinidine in biologic samples. They demonstrated that quinidine exhibits a fluorescence in acid media which can be measured in a Coleman photofluorometer. Further details of the method have been described.[6-8] We have used the extraction technique of preparing the sample.

Utilizing Brodie's method, Delevett and Poindexter[9] were able to show that in two patients with recurrent nodal tachycardia attacks were absent at plasma quinidine concentrations exceeding 1 mg. per liter, but recurred when the concentration was less than this. Wegria and Boyle[10] noted the relation between the fall in auricular rate and the blood quinidine concentration and found the correlation grossly but not quantitatively parallel. They also observed variable concentrations of quinidine obtained in different individuals receiving the same dose. Linenthal, Ulick, and Patterson[6] concluded that the plasma concentration could be used as a guide to the intensity of the action of quinidine on the heart. Hiatt[11] determined the plasma concentration of quinidine following single oral doses of the cinchona alkaloids and noted considerable variations between quinine and quinidine, as well as variations among individuals.

As a guide to the concentration of quinidine that might be effective therapeutically, Hiatt and associates[12] demonstrated that quinidine produced a complete vagal block in dogs at a concentration averaging 7.4 mg. per liter. As will be seen later, therapeutic concentrations in man approach this figure. Hiatt and associates determined the concentrations of quinidine in the tissues of various organs in dogs and correlated them with the concentration in the blood. They found that the tissue/plasma ratios at various plasma concentrations were essentially the same. Of interest is the fact that the highest tissue concentrations were found not in the heart but in the glandular organs (liver, kidney, spleen) and in the lung. Our own observations in a limited number of studies in man are confirmatory. Hiatt found that the concentration of quinidine was relatively low in the cerebrospinal fluid, red blood cells, brain, skeletal muscle, and bile. We have found it relatively low in bile and pleural fluid in man in the few studies made. Wegria and Boyle[10] also noted that the concentration of quinidine was much higher in the heart muscle and kidney than in the plasma and that the highest tissue concentration was reached at the peak of the plasma concentration. The clinical studies of Kalmansohn and Sampson[13] and of Sokolow and Edgar[7] are not strictly comparable because the former used the precipitation technique

rather than the extraction technique in preparing the samples for determining quinidine concentration. The former technique results in somewhat higher readings,[8] and in the comparison of data this fact should be noted.

Clinically, knowledge of blood levels has been of value in two important ways in using quinidine for conversion of arrhythmias. First, blood levels aid the physician in determining whether the dosages can be continued or increased in instances where the arrhythmia fails to convert or recurrent arrhythmias are not prevented. This situation occurs when the blood concentration is relatively low, despite an average dose of quinidine. In ninety-three instances of chronic auricular fibrillation in which conversion occurred, the blood concentration of the patients averaged 5.4 mg. per liter. If 2 or 3 Gm. of quinidine given over a ten-hour period do not result in conversion and if the blood concentration is only 4 to 6 mg. per liter, the dosage can be increased safely and with some confidence, provided evidence of toxicity, clinically or electrocardiographically, is not present. Significant toxicity (conduction defects, ventricular arrhythmias) is infrequent at levels below 6 to 8 mg. per liter, although vomiting or diarrhea may occur at levels of approximately 4 to 6 mg. per liter. Second, from the concentration of quinidine in the blood, the time when a dosage should not be increased can be decided. If the concentration is high (9 to 10 mg. or more per liter) on average doses (2 to 3 Gm. in ten hours), especially in older patients with severe cardiac disease, particular caution should be used in increasing the dose of quinidine, even though no evidence of toxicity has been noted. The possibility of toxicity increases when the blood concentration of quinidine exceeds 9 to 10 mg. per liter and the likelihood of successful conversion decreases, although we have attained conversion in patients with levels varying from 10 to 15.8 mg. per liter. Since peak levels occur two hours after the last dose, blood levels are best obtained at that time.

Not all arrhythmias convert at the time of the maximum blood concentration; in about 15 per cent of the patients, conversion occurs during the night, when the blood concentration is falling. The explanation for this occurrence is not clear, but it indicates the need for being certain that regular rhythm has not been restored during the night before starting larger doses of quinidine the following morning. Even though conversion may not occur at the time of the peak level, it appears necessary to attain this peak concentration in order to achieve the conversion which occurs later when the concentration is decreasing. For example, a concentration of 5 mg. per liter might not result in conversion if it were the peak level, but conversion might occur at a level of 5 mg. per liter if a level of 7 mg. per liter had been achieved six to eight hours previously.

Finally, if the compensation of the heart is impaired or if the nervous tension of the patient varies greatly, successful conversion may not occur until these are controlled. Sedation is valuable if the patient is apprehensive. On occasion, in a patient who was given large doses while residual cardiac failure persisted but in whom conversion did not occur, successful conversion resulted following smaller doses on a second attempt after compensation had been restored by vigorous therapy.

III. MOST EFFECTIVE METHOD FOR ADMINISTRATION OF QUINIDINE

Every cardiologist has a favorite method for the administration of quinidine. The methods vary. According to some, quinidine should be given every hour; others believe quinidine should be given every two to four hours day and night, or every two hours for four to six doses, or that there should be stepwise increments with each dose.

Experience with determinations of the level of quinidine in the blood has clarified some of the controversial issues and explained the ineffectiveness of certain dose schedules. Data obtained from a variety of methods (auricular rate,[14] Q-T interval,[4,15] and blood levels[6,7,10,11,13]) have indicated that, with a single dose of quinidine taken orally, the effect is at its peak in two to three hours, begins to subside in four hours, is about half dissipated at eight hours, and usually has ceased at twenty-four hours. Slowing of the auricular rate in fibrillation roughly parallels, although not quantitatively, the rise in blood concentration.[7,10] The concentration of quinidine in the blood in general effectively parallels the cardiac effects of the drug, and restoration of normal rhythm and maximum fall in auricular rate usually occur at the time of the peak blood concentration.

The frequency of administration is important in the effective use of quinidine. Since the peak effect occurs within two hours, a two-hour dosage interval is logical; in addition, it has proved effective in producing progressive and significant rises in blood concentration and cardiac effects. But cumulation ceases, and the blood concentration no longer rises after a certain number of doses at two-hour intervals. Five two-hour doses have been found to be the most effective number.[6,7] After five doses, if administration is continued at the same time intervals, metabolic breakdown keeps pace with the additional drug intake, so that the blood concentration does not usually rise farther. When quinidine is given every four hours during the day, or during the day and night, cumulation usually ceases after forty-eight to seventy-two hours, and continuance of the dose at the same interval produces no further increase in blood concentration. Occasionally, with the same fixed dose at four- to six-hour intervals, peak levels are reached after four to five days; rarely, the effect may be parabolic, so that the level at seven to fourteen days is lower than that at three days.

It has been established that quinidine levels are almost zero twelve to twenty-four hours after a single dose of the drug,[6,10,11] yet if quinidine is given every two hours for five doses, a blood level averaging about 40 per cent of the peak level (reached after the fifth dose) can be expected twelve hours after the last dose.[7] Because of this morning residual level, administration of quinidine every two hours for five doses for several successive days permits gradual increase in blood concentration of the drug without the need of resorting to higher doses. It is not necessary to build up the level anew each day. Conversion may be successful, therefore, after several days of this same dosage.

Individual variation in blood concentration achieved with any given dose of quinidine also must be appreciated. For example, if quinidine is given in a dosage of 0.4 Gm. four times a day, the peak level after three days may vary from 3 to 10 mg. per liter in different individuals.

With these data in mind, if it is decided to use quinidine to cause conversion in an average case of an arrhythmia, either of the following techniques* which have proved effective and satisfactory may be utilized:

(1) A dosage of 0.2 or 0.4 Gm. every two hours for five doses on the first day, either repeated or increased by 0.2 Gm. per dose on the second and third days, depending on the successful conversion or presence of toxicity (see Section V). If conversion does not occur after administration of 3 Gm. of quinidine in ten hours each day for three days, higher doses can be used, provided blood levels are below 8 to 9 mg. per liter and there are no significant ventricular premature beats, electrocardiographic changes, hypotension, vomiting, or severe diarrhea. Levels above 9 mg. per liter or doses totaling more than 3 Gm. a day should be attempted with particular care, although successful conversion has occurred in 50 per cent of the fifteen instances in which quinidine was increased beyond these figures. If conversion does not occur with 4 Gm. in ten hours each day for three days, or with a blood level of 11 mg. per liter or more, the likelihood of conversion decreases from 80 per cent at the outset to about 30 per cent. If conversion is urgently required and no evidence of severe toxicity has occurred, 5 Gm. in ten hours can be given. A dosage of 6 Gm. is the highest we have used and is not advised except in urgent situations.

(2) A dosage of 0.2 or 0.4 Gm. four times a day for seventy-two hours. If conversion does not occur and no severe toxicity has developed, the dose can be increased 0.2 Gm. every seventy-two hours. This increment results in a dosage of 0.6 Gm. four times a day on the fourth day and 0.8 Gm. four times a day on the seventh day. With this technique, the blood level is increased more slowly, permitting treatment in occasional cases where rapid administration of the drug (every two hours for five doses) results in vomiting. At times, the slow administration has been ineffective, whereas giving the drug more rapidly has been effective.

IV. THE USE OF DIGITALIS PRIOR TO ADMINISTRATION OF QUINIDINE IN AURICULAR FIBRILLATION

Lewis[14] was the first to emphasize that digitalis should be used to slow the ventricular rate before administration of quinidine in auricular fibrillation. Quinidine decreases vagal tone,[12,16] as well as prolonging the refractory period of auricular muscle,[4] and the ventricular rate may become rapid under the influence of quinidine if digitalis is not used or if the patient is incompletely digitalized. In the 1920's, before this principle was fully appreciated, it was often found necessary to discontinue the drug because of rapid ventricular rates in patients receiving quinidine for conversion.[17] The need for digitalis does not obviate the necessity of avoiding overdigitalization, since Gold[4] has shown that the combination of toxic doses of digitalis and quinidine is highly undesirable. It is our practice to digitalize all patients with chronic auricular fibrillation before using quinidine

*The patient should be in bed in the hospital so that careful observation can be carried out. In addition, in order to exclude sensitivity to quinidine, a test dose of 0.1 or 0.2 Gm. should be given prior to institution of formal therapy. If no reaction occurs within four hours, the regular schedule of doses can be employed.

and to maintain digitalis saturation during therapy with quinidine; we have observed no untoward results because overdosage with digitalis and toxic doses of quinidine were avoided. The experience of McMillan and Welfare[18] and Goldman[19] has been the same as ours.

V. THE HAZARDS OF AURICULAR FIBRILLATION PER SE

Before discussion of the indications and contraindications of quinidine in auricular fibrillation, it is profitable to consider the hazards of auricular fibrillation per se. This arrhythmia is not innocuous, despite the fact that many patients live comfortably for many years with a ventricular rate well controlled with digitalis. Various writers[1,17,18,20-24] have indicated that the major hazards of chronic auricular fibrillation are: (1) pulmonary and systemic embolism, (2) sudden death, and (3) progressive cardiac enlargement with ultimate cardiac failure.

In the great majority of instances, embolism in mitral stenosis occurs in the presence of auricular fibrillation.[25,28] Mattingly and associates[25] reported that of 167 patients with rheumatic heart disease who had peripheral emboli, auricular fibrillation was present in 90 per cent. Every year we see patients with cerebral or femoral emboli associated with auricular fibrillation; some die; others remain seriously handicapped or lose a leg. Hall[26] noted that of 257 patients with auricular fibrillation who died, 42 per cent had one or more emboli. Ten to 20 per cent of all deaths in rheumatic heart disease result from emboli (Lewis and co-workers[27] and Laws and Levine[28]). Weiss and Davis[29] found that emboli caused death in 16 per cent of 164 deaths from rheumatic heart disease. Sudden death may occur in any patient with cardiac disease, but it is not generally appreciated that 2.5 to 4 per cent of patients with auricular fibrillation die suddenly and unexpectedly.[1,20,21,30]

The decrease in functional capacity of the heart which results from auricular fibrillation, even when ventricular rates are well controlled, has not been fully appreciated. It has been demonstrated experimentally in dogs that, when auricular fibrillation is produced, the cardiac output decreases approximately 40 per cent,[31] the blood flow is decreased 20 to 62 per cent,[32] the size of the heart increases,[33] and the central venous pressure after exercise rises disproportionately as compared to the rise after exercise in dogs with sinus rhythm.[34] Blumgart[35] has demonstrated that the increase in ventricular rate after exercise is greater and the return to the resting level is slower in patients with auricular fibrillation than in patients with sinus rhythm, even though they have been digitalized. Isolated case reports[1,36] have shown clearly that cardiac enlargement and congestive failure can occur in patients with auricular fibrillation but with no organic heart disease and that this cardiac failure may be reversible if normal rhythm is restored. The most complete and convincing study was recently reported by Phillips and Levine,[37] who demonstrated frank or latent cardiac failure in fourteen of eighty-four patients with auricular fibrillation who had no organic heart disease. The circulatory dynamics, cardiac size, and competence changed toward normal after conversion to sinus rhythm. It is of great interest that cardiac

failure usually developed in a matter of weeks to months after the onset of auricular fibrillation, but if the arrhythmia was tolerated without difficulty for a year, subsequent cardiac failure was unusual.

VI. THE BENEFITS OF CONVERSION OF AURICULAR FIBRILLATION

Distinct benefits accrue to many patients with chronic auricular fibrillation in whom conversion is successful, entirely apart from the advantage of prevention of the hazards mentioned previously. The most important gain is the increase in exercise tolerance and the ability to return to a more active life. Although this benefit has been noted in the literature,[7,14,21,38] it has not been adequately emphasized. We have seen patients with severe chronic congestive failure, which was not relieved despite prolonged bed rest, full digitalization, low-sodium diet, and frequent mercurial diuretics, become completely compensated following restoration of sinus rhythm. One such patient, who required complete bed rest in the hospital for three months, became ambulatory and no longer needed diuretics following conversion. At times, patients find they can do more, even though obvious signs of cardiac failure were not present prior to conversion. Improvement is often impressive.

Earlier investigators[39] demonstrated an increase in cardiac output following conversion, but the reliability of their methods has been questioned. Within the last year, two groups of investigators[40,41] have demonstrated an increase of about 40 per cent in cardiac output at rest following conversion in patients who had chronic auricular fibrillation and heart failure. If heart failure was not present or if it was minimal, the cardiac output did not increase after conversion, or did so only after exercise. This proof of increased cardiac output following conversion in patients with cardiac failure provides important documentation to support the clinical evidence of the striking benefits of conversion.

The relief from disturbing palpitations following conversion may be considerable in some patients who have had palpitations despite full digitalization.

VII. THE HAZARDS OF CONVERSION WITH QUINIDINE

It is a truism to say that quinidine is a protoplasmic poison and therefore toxic. Most patients can take therapeutic doses of the drug, either for conversion of an arrhythmia or prevention of recurrent arrhythmias, with, at most, only minor cinchonism. Apprehension, nausea, tinnitus, mild diarrhea, and headache are the most common symptoms and may occur occasionally, even with average or small doses. Vomiting, more severe diarrhea, and dizziness are more substantial symptoms, although they have not led to any serious consequences. Vomiting, the most important of the relatively "minor" toxic manifestations, frustrates successful conversion in a fair percentage of patients, even, at times, when the drug is given intramuscularly. In the 20 per cent of the patients with chronic auricular fibrillation in whom conversion did not occur following the use of quinidine, vomiting was the most common cause of the failure. Amblyopia has been described, but in my experience its occurrence has been unusual.

Idiosyncrasies do occur, although fortunately they are rare. Diarrhea or vomiting may appear after the first few doses, precluding further treatment. Fever,[42] thrombocytopenic purpura,[41] and rashes[15] have been described, but are extremely rare. Test doses of 0.1 to 0.2 Gm. have been advised and used because of these possibilities. Dawson and co-workers[44] have demonstrated that coryza may be a manifestation of the sensitivity of a patient to quinine but that an individual with this reaction may tolerate quinidine satisfactorily.

Systemic embolism often has been attributed to conversion with quinidine, but practically all recent publications state this hazard to be greatly overemphasized.[1,21,22,26] Hall[26] found 808 instances of auricular fibrillation in 2,500 cases of heart disease. Emboli were demonstrated clinically in 132 and at autopsy in fifty-six of the 508 patients not receiving quinidine. Emboli occurred in nine of 337 patients with auricular fibrillation who were taking quinidine; the incidence of emboli was ten times as great in patients with auricular fibrillation who did not receive quinidine. Viko and associates[22] demonstrated a slightly greater incidence of emboli in untreated patients than in patients treated with quinidine. Fahr[38] encountered no emboli in 500 patients with auricular fibrillation treated with quinidine. In forty-four instances of successful conversion in McMillan and Welfare's[18] series and in ninety-three of my own series, no emboli occurred with or immediately after conversion. On several occasions, we have observed that when auricular fibrillation recurred, either because of inadequate maintenance treatment with quinidine or cessation of the drug, emboli appeared. Fahr[38] has emphasized this same point. Goldman,[19] in sixty-seven cases of auricular fibrillation converted by the technique advocated by the author, observed two instances of emboli following therapy with quinidine. One patient, 58 years old, four hours after conversion to sinus rhythm, developed a motor aphasia that lasted forty-eight hours. A second patient, 70 years old, who had cardiac failure, developed a left hemiplegia several hours after sinus rhythm was re-established. This incidence of emboli after conversion in 3 per cent of the patients in Goldman's series is in contrast to the fact that 27 per cent of his patients had a history of emboli while fibrillating prior to the establishment of regular rhythm.

Sudden death is a hazard of quinidine therapy, but fortunately it is extremely rare. Askey[21] has analyzed the literature well and tabulated all known instances of death from quinidine. Autopsies in these cases have rarely shown cause for sudden death,[45] and it must be presumed to have been due to ventricular fibrillation or cardiac asystole. Respiratory paralysis is a possibility.[46] The data presented by Cookson[20] and Askey[21] make it clear that sudden death as a result of the drug is a distinct although rare possibility. Many deaths, however, have been unjustifiably attributed to quinidine. For example, in one patient treated by a colleague, sudden death occurred two days after conversion of chronic auricular fibrillation. Death was at first attributed to quinidine, until autopsy revealed a cerebral embolus secondary to vegetations on the aortic valve in a case of unsuspected subacute bacterial endocarditis.

In our series of 119 attempted conversions, only one patient died suddenly. This woman had severe mitral stenosis and cardiac failure; because of inability to control the failure with the standard procedures, conversion was attempted.

After moderate intramuscular doses of quinidine (1.6 Gm. in eight hours) and when the blood level had reached about 7 mg. per liter, ventricular tachycardia resulted. It subsided spontaneously, but four hours later the patient developed ventricular fibrillation and died suddenly. No explanation for the sudden death was found at autopsy. Levine[46] described a similar case and commented that in his experience the serious effects due to quinidine have occurred particularly in patients with mitral stenosis. Sampson[58] has had the same experience. Goldman[19] had one death in his series of cases, also in a patient with mitral stenosis.

Asystole, which has been feared by Gold[4] as a hazard in quinidine treatment, seems less frequently the mechanism of sudden death than ventricular fibrillation.[38] Korns,[23] in an experimental study, noted that all dogs in his series died of ventricular fibrillation, with respiration stopping a few minutes before death. Transient auricular standstill was noted in two patients by Wolff and White after conversion to sinus rhythm.[47] In a few of our patients nodal rhythm occurred, without clear evidence of auricular activity, at the height of quinidine effect. The patients had no clinical symptoms at the time, and as a rule sinus rhythm returned after about twenty-four hours. No untoward effects were noted, although it seems clear that the sinus node is more readily depressed by quinidine than the atrioventricular node. It is, of course, possible that if the atrioventricular node did not assume command, the patient would have to depend on the ventricular pacemaker to prevent cardiac standstill. Goldman[19] observed nodal rhythm following conversion of chronic auricular fibrillation with quinidine in 8 per cent of his patients.

VIII. VENTRICULAR ARRHYTHMIAS

In our opinion, ventricular arrhythmia is as important, if not more important, a toxic effect of quinidine on the heart as are conduction defects. It is a paradox that quinidine can both relieve and induce ventricular arrhythmias. Ventricular premature beats, occurring in runs, may develop when the quinidine concentration in the blood exceeds 6 mg. per liter and are an indication to stop administration of the drug. We have experienced this evidence of toxicity in only five patients. An occasional ventricular premature beat is not uncommon and cannot be clearly ascribed to quinidine, but, if noted, further doses should be used cautiously. Wilson and Wishart[48] gave small intravenous doses of quinidine (0.2 Gm.) to patients with auricular fibrillation and noted ventricular premature beats in a considerable number of patients; in several instances, runs of three or more beats occurred.

Ventricular tachycardia has occurred in two of our 111 patients with auricular fibrillation in whom conversion with quinidine was attempted; in three others, short runs of ventricular premature beats occurred. In one instance of ventricular tachycardia, large doses of the drug and high blood levels were necessary for conversion. This patient had severe mitral stenosis; quinidine was "pushed" because the patient was a "cardiac cripple," completely invalided by his disease, and because he had had two previous major embolic accidents. A quinidine blood concentration of 15.6 mg. per liter was achieved, at which time ventricular

tachycardia occurred; it lasted three hours, after which sinus rhythm resulted. The patient was maintained in regular rhythm in comfort and was ambulatory for at least a year. The second patient, who developed ventricular fibrillation four hours after ventricular tachycardia had stopped, has been described previously. An electrocardiogram during the terminal episode revealed ventricular fibrillation.

Ventricular premature beats and even short runs of ventricular tachycardia may be overlooked unless frequent clinical examinations of the patient are made. We have observed frequent runs of premature beats which were not present on an electrocardiogram taken a short time later, only to note their recurrence an hour after the electrocardiogram was taken. At times, patients complain of weakness and dizziness, which may be due to premature beats that are transient. These symptoms, however, may be due to hypotension.

IX. HYPOTENSION

Ferrer and associates[49] found that a vasodepressor effect was the most common hemodynamic result of quinidine in subjects studied by cardiac catheterization. These authors demonstrated a fall in arterial pressure in twelve of eighteen normal subjects after single doses of 0.8 Gm. of the drug. This fall was not associated with any change in cardiac output or right ventricular pressure. A fall in blood pressure of 10 to 20 mm. Hg. is not uncommon in patients receiving therapeutic doses of quinidine by the oral route, but as a rule no important fall in blood pressure occurs unless the dosage is high or the drug is given parenterally, especially intravenously.

Recently, in a woman who developed nodal tachycardia, with a ventricular rate of 180, two days after a mitral valvulotomy, treatment was complicated by the fact that the onset of the tachycardia precipitated shock; the systolic blood pressure was 60 mm. Hg. Quinidine gluconate (Lilly), 0.4 Gm. given intramuscularly at two-hour intervals, resulted in conversion to sinus rhythm in four hours; the blood concentration was 6.4 mg. per liter. The management of ventricular arrhythmia in the presence of hypotension is indeed difficult, but the physician will be more secure in the knowledge that ordinary doses of quinidine given orally usually will not lower the blood pressure further.

X. INTRAVENTRICULAR CONDUCTION DEFECTS

The earliest effect of quinidine, as determined electrocardiographically, is an increase in the Q-T interval. Sagall and co-workers[15] used this finding to compare the effects of quinine and quinidine. With increased dosage and higher blood concentration of quinidine, the QRS complex may become widened and slight ST-T abnormalities may appear. With progressively larger doses, both in dogs[23] and in man,[4,7,19,50] the QRS complex may widen progressively to typical bundle branch block with QRS intervals as wide as 0.2 second. Usual doses of quinidine (2 to 3 Gm. a day) do not increase the QRS interval significantly, although increases from 25 to 50 per cent may occur as the blood concentration exceeds 7 mg. per liter.[59] Many patients show no change in the QRS duration despite full therapeutic doses of quinidine. In patients with myocardial infarc-

tion who were receiving 0.4 Gm. of quinidine four times a day prophylactically and in whom the average midday level was 5 to 6 mg. per liter,[51] no instance of intraventricular conduction defect was initiated by the drug. In one case of incomplete left bundle branch block with a QRS interval of 0.12 second, complete left bundle branch block with a QRS interval of 0.16 second occurred with doses of 0.4 Gm. four times a day. Increases of QRS duration up to 25 per cent of the control measurement have been stated by Gold[4] to be safe. Our experience coincides, and we have observed normal QRS intervals to widen to as much as 50 per cent without significant clinical toxic effects, other than cinchonism.[51,59] In one instance, the QRS widened to 0.2 second; this maximum effect occurred in a patient with auricular fibrillation and mitral stenosis who was severely limited by his arrhythmia, and the drug was "pushed," with frequent clinical and electrocardiographic observations. By means of the drug, the auricular rate was decreased from 500 to 136 a minute and the QRS widened from a control value of 0.09 second to 0.20 second, at which time quinidine was stopped. It was of interest that the widening of the QRS interval decreased in three hours as the blood concentration of quinidine became less; at no time did ventricular premature beats or ventricular tachycardia appear.

The degree of widening of the QRS complex to be permitted before discontinuing use of quinidine is not established. Theoretically, slowing of intraventricular conduction may be followed by ventricular asystole or fibrillation if quinidine is not stopped. As a rule, we have not pursued therapy after the increase in the QRS time exceeded 50 per cent of the control value, and we have used particular caution when the increase in QRS duration exceeded the 25 per cent recommended by Gold.[4] In all cases, the original QRS duration was reestablished within twenty-four hours. QRS intervals exceeding 0.14 second (an increase of more than 50 per cent of the control QRS interval) occurred in nine of our patients receiving quinidine for conversions of auricular fibrillation. Blood levels in these patients varied from 8.5 to 17 mg. per liter. In three of these nine patients, the intensity of the quinidine effect was also noted by the fact that auricular tachycardia (auricular rates 136, 120, 138), with 1:1 conduction, was associated with the wide QRS complex.

The use of quinidine in patients who have intraventricular conduction defects or bundle branch block poses a special problem. Barker, Johnston, and Wilson[52] described transient right bundle branch block in a normal subject after single oral doses of 0.4 Gm. of quinidine sulfate. This is a most unusual event, however. Gold[4,50] noted no significant increase in QRS duration in patients with intraventricular conduction defects who were receiving relatively small daily doses of quinidine (1 to 2 Gm.).

We have attempted conversion of auricular fibrillation in the presence of bundle branch block in only one case. In this patient, conversion did not result at a blood level of 7 mg. per liter and the attempt was abandoned, although no evidence of toxicity was noted. We[51] have given quinidine to two patients with chronic auricular fibrillation and bundle branch block in order to control runs of ventricular premature beats; in both patients sinus rhythm was unexpectedly restored, and in one of the two the QRS interval became normal following con-

version. In five other instances of bundle branch block in patients suffering from acute myocardial infarction, 0.4 Gm. of quinidine was given four times a day; no increase in the QRS interval resulted except in the one patient with incomplete left bundle branch block mentioned previously.

Goldman[19] attempted conversion in nine patients with intraventricular conduction defects (six of whom had bundle branch block). Successful conversion occurred without incident in the six patients with bundle branch block and in one of the other three patients. In a patient from a nearby hospital, quinidine was given for conversion despite the presence of right bundle branch block. At a level of 6 to 7 mg. per liter, complete atrioventricular dissociation resulted, with Stokes-Adams attacks. Several hours later, a short run (20 beats) of ventricular tachycardia developed. It appears, then, that in the eighteen patients described, serious toxicity occurred in only one patient. Nevertheless, it is obvious that this experience is too limited to allow proper evaluation of the risk of using quinidine in the presence of an intraventricular conduction defect. It would appear, however, that the presence of an intraventricular conduction defect or bundle branch block should be considered a relative, but not an absolute, contraindication to the use of the drug should the clinical condition of the patient warrant its use.

XI. ATRIOVENTRICULAR DEFECTS

Complete atrioventricular block has been considered an absolute contraindication to therapy with quinidine. Documented experience is very limited in regard to the use of quinidine in either partial or complete atrioventricular block. Parkinson and Campbell[1] described one patient in whom the administration of quinidine produced cyanosis and coma, but did not cause death. The only patient with complete atrioventricular dissociation in our series[51] was an individual suffering from acute myocardial infarction who developed the block shortly after entering the hospital. He also had auricular fibrillation. The morning after admission to the hospital, he developed ventricular tachycardia; sinus rhythm was restored at a blood concentration of 6.3 mg. per liter after the patient had received quinidine gluconate (Lilly), 0.8 Gm. intramuscularly.

Partial atrioventricular block was observed in at least 15 per cent of our series immediately after sinus rhythm was restored. The P-R interval was usually only slightly prolonged (0.22 to 0.26 second). In two instances complete atrioventricular dissociation resulted from treatment with quinidine, in one at the time of conversion and in the other without conversion. Stokes-Adams attacks did not occur, and the dissociation was no longer present the following day.

The data from the literature are insufficient to assess the risks of cardiac standstill resulting from treatment with quinidine in ventricular arrhythmias associated with partial or complete atrioventricular block. The hazard must be significant, and quinidine should probably not be used unless the clinical condition of the patient forces one to do so.

XII. DEVELOPMENT OF AURICULAR FLUTTER

Lewis and associates[27] stated that if auricular flutter develops during the treatment of auricular fibrillation with quinidine, the drug probably should be

stopped because of the danger of developing a 2:1 or 1:1 flutter. If a patient, while in auricular fibrillation, had an auricular rate of 500 and a ventricular rate of 70, Lewis feared that as the auricular rate slowed to 200 or 300, the ventricular rate might rise to 150 or 200, with disastrous clinical effects. Wilson and Wishart[48] noted that quinidine given intravenously to patients with auricular fibrillation frequently resulted in impure flutter or, more rarely, in pure flutter. They stated that the rate of conduction was apt to be 2:1 when the auricular rate was approximately 300 and that 1:1 conduction was likely if the auricular rate fell below 300. Drury and Iliescu[53] also emphasized that under the influence of quinidine, auricular fibrillation changes to sinus rhythm via a stage of impure flutter. They advised not lowering the auricular rate below 200 because of the danger of 1:1 conduction, with resultant rapid ventricular rates.

In our own experience, we have found that most patients passed through a stage of auricular flutter, with regular auricular oscillations of about 240 to 300 a minute. Only infrequently (perhaps as a result of inadequate digitalization) did a 2:1 conduction appear with a ventricular rate of about 130. Quinidine was usually continued and sinus rhythm developed. If the patient is adequately digitalized before treatment with quinidine, the occurrence of rapid ventricular rates as the auricular rate slows is infrequent, unless one has misjudged the adequacy of the digitalization. At times, a patient with a casual ventricular rate of 70 to 80 who was thought to be adequately digitalized was found to be inadequately digitalized when the ventricular rate rose to 120 during treatment with quinidine. In these cases, increasing the amount of digitalis slowed the ventricular rate. In some patients with auricular fibrillation, if administration of quinidine is "pushed," the auricular rate may progressively slow to the point where the rhythm resembles auricular tachycardia, with auricular rates varying from 120 to 180. One may note progressive changes through stages of auricular fibrillation, auricular flutter, and auricular tachycardia as the auricular rate progressively slows. The reverse occurs when quinidine is stopped.

Goldman[19a] recently reported the appearance of auricular flutter in 70 per cent of his cases of auricular fibrillation during treatment with quinidine, and his experience with the rarity of the development of 2:1 or 1:1 auricular flutter coincides with mine. As noted in Section X, we have observed 1:1 conduction in three patients who developed auricular tachycardia with auricular rates of approximately 138 as a result of treatment with quinidine. We have not observed this condition when the auricular rates were faster and could be classified as auricular flutter.

To illustrate the need for not fearing further use of quinidine when auricular flutter has resulted from its use, the following case can be cited. In this patient, the dose of quinidine was decreased when auricular flutter was noted in the electrocardiogram at a blood concentration of 8 mg. per liter. After a week of smaller doses, it was decided to ignore the appearance of the flutter; the dose of quinidine was increased, and the flutter was again noted at a blood level of 8 mg. per liter. Quinidine was continued, however, and eight hours later, when the blood concentration was 9.3 mg. per liter, sinus rhythm occurred. It is our belief that auricular flutter represents a stage which must be passed, as the auricular

rate slows during the course of treatment of auricular fibrillation with quinidine. The drug should be continued rather than stopped in such cases because, as a rule, conversion to sinus rhythm is nearly achieved when the auricular rate falls to the 180 to 250 range. Rarely, when large doses of quinidine are used, the auricular rate may fall to 120 to 150 a minute. In our experience, when the auricular rate fell to this degree, evidence of toxicity, such as widening of the QRS complex, ventricular premature beats, or 1:1 conduction, usually forced cessation of quinidine. A fall of this degree in the auricular rate without conversion to sinus rhythm is an indication that conversion probably will not result. In most patients with auricular fibrillation, conversion to sinus rhythm occurs when auricular rates exceed 180 to 200 a minute.

XIII. THE PROVOKING OF CARDIAC FAILURE

Fahr[18] discussed the appearance of cardiac failure following treatment of auricular fibrillation with quinidine in patients who did not have failure before treatment. He had previously believed that quinidine could provoke cardiac failure, but later, in his excellent paper of 1938,[18] stated that when his patients with auricular fibrillation were properly digitalized before treatment with quinidine was begun, cardiac failure did not occur. Our experience agrees with that of Fahr; we have not seen cardiac failure appear for the first time as a result of treatment with quinidine, nor have we encountered a patient in whom the ventricular rate after conversion to sinus rhythm was rapid and uncontrollable. As a rule, if a patient with auricular fibrillation has a ventricular rate of 70 to 80 while receiving digitalis, the heart rate is essentially the same or often distinctly lower after conversion. Indeed, the ventricular rate often varies from 80 to 95 a minute before conversion and frequently approaches 70 a minute after conversion. We have seen instances when the ventricular rate could not be lowered below 110 to 120 a minute, even when digitalis was increased to the point of toxicity; following restoration of sinus rhythm, the ventricular rate was 70 to 80 a minute. It is conceivable the ventricular rate may be controlled more easily in a patient while he has auricular fibrillation than while he has sinus rhythm, but such a situation must be very rare, and the fear of such an eventuality should certainly not deter one from attempting conversion.

XIV. WHICH CASES OF CHRONIC AURICULAR FIBRILLATION SHOULD BE CONVERTED?

This is a highly controversial subject. Opinions vary from Gold's,[4] "Treatment of chronic auricular fibrillation with quinidine has been largely abandoned," to McMillan and Welfare's,[18] "All patients with chronic auricular fibrillation, except those with severe conduction defects, subacute bacterial endocarditis, or angina pectoris which has been previously relieved by the appearance of auricular fibrillation, should be given a trial of quinidine." Sample quotations from standard texts and reference works on medicine indicate that conversion with quinidine should be attempted: if the patient has "no congestive failure or serious heart disease or history of embolism" (White[54]); in "those fibrillators

without organic heart disease, those fibrillators who continue to show auricular fibrillations 2 weeks or so after a subtotal thyroidectomy for hyperthyroidism when the basal metabolic rate has returned to normal" (Levine[46]); "Quinidine is usually not preferred or is contraindicated in cases of chronic cardiac disease or heart failure, long-standing auricular fibrillation and cardiac enlargement" (Friedberg[55]); "Quinidine conversion should not be attempted (1) if fibrillation has been present for a long time..., (2) if the heart is large, (3) during heart failure..., (4) if failure has been of long duration, (5) without taking into consideration that some patients feel better and the heart rate is more easily controlled during fibrillation" (Stewart[56]); "If in any given case the underlying condition is such that the patient would not likely be any better off with a normal rhythm with the sinus rate more rapid than the ventricular rate under control by digitalis, then such a drug should be withheld" (Kerr and Lagen[57]).

On the other hand, McMillan and Welfare,[18] Sampson,[11,58] Fahr,[58] Goldman,[19] Askey,[21] Sokolow and Edgar,[7] and others have emphasized that striking improvement without toxicity may occur in the patient with advanced cardiac disease. Thus, if the advice quoted from the texts were used, quinidine would be withheld from the very patients with chronic auricular fibrillation who might benefit most from conversion.

The hesitancy in using quinidine for conversion is based essentially on fear of embolic accidents and sudden death. These hazards were discussed in a previous section. No one can deny that in rare instances, and even in a patient with minimal heart disease and fibrillation of short duration, a serious accident may follow the administration of quinidine. Much of the fear, however, has resulted from a carry-over from the unfavorable results two to three decades ago when quinidine was given to all patients with auricular fibrillation, often without treatment of the cardiac failure present, without prior digitalization, and in critically ill patients.

Probably a better evaluation of the degree of risk can be obtained from study of the three recent series of more than 200 patients commented upon previously.[18, 19,59] In these patients, unexpected death occurred in two, emboli in two, and ventricular tachycardia or short runs of ventricular premature beats in five; obviously, risks to life are relatively small in relation to the possible benefits, provided modern technique is used and careful observation of the patients is carried out. The low incidence of serious toxicity is even more striking when one notes the high percentage of successful and safe conversion in patients who had (1) previous emboli, (2) cardiac enlargement, (3) long-standing auricular fibrillation, and (4) previous cardiac failure. In Goldman's[19] series, 26 per cent of the patients had marked cardiac enlargement, 27.5 per cent had previous emboli, a "majority" had congestive heart failure at the time of admission to the hospital, and nine had bundle branch block; nevertheless, he obtained conversion in 83 per cent of his eighty patients. Our own series included a group of comparable patients with conditions previously thought to represent "contraindications."

The reversal of opinion of leading authorities in regard to treatment with quinidine of patients with previous emboli is of interest. Practically all articles

and texts prior to 1940 concurred with the statement of Parkinson and Campbell[1] that quinidine was contraindicated in patients with chronic auricular fibrillation who had a history of embolism. The literature was summarized in 1939 by Sokolow,[60] who described a patient with multiple recent emboli in whom successful conversion occurred as a result of the use of quinidine. In 1942, White and Blumgart[61] reported on two similar cases. In 1944, with quinidine and quinine in short supply, the National Research Council,[62] in describing the indications for quinidine, listed "a history of systemic embolization in a case of paroxysmal or established auricular fibrillation." In the three series of approximately 200 cases described previously,[18,19,59] only two instances of embolic accident occurred following conversion to sinus rhythm. Neither of these two patients had had emboli prior to conversion. No new emboli occurred in those patients who gave a history of emboli prior to conversion. This experience would seem to support the conclusion of the National Research Council that previous emboli are an indication, rather than a contraindication, to treatment with quinidine. On theoretical grounds, Goldman,[19] as well as the author and others, has used Dicumarol for two weeks before administering quinidine, but whether this is necessary is uncertain.

The matter of whether to convert auricular fibrillation when it occurs in patients with mitral stenosis deserves special mention. In our experience, chronic auricular fibrillation can be successfully converted with quinidine in 80 per cent of a miscellaneous group of patients, whereas the percentage falls to approximately 50 per cent in patients with mitral stenosis. Goldman's[19] experience was similar. In McMillan and Welfare's[18] series, however, the results in patients with mitral stenosis were as successful as those in patients with auricular fibrillation of other etiology; they had only one failure in twenty-three cases of rheumatic heart disease in which conversion was attempted. Levine[46] described the occurrence of sudden death in a patient with mitral stenosis during treatment with quinidine and concluded that the value of quinidine in mitral stenosis is questionable. Fahr[38] stated that all patients with mitral stenosis should be given a trial of quinidine, provided the enlargement of the heart is less than 20 per cent and the arrhythmia is of less than 6 months' duration. Askey and Cherry[63] presented data showing that nine of thirteen patients with mitral stenosis developed cardiac failure when auricular fibrillation developed; in their opinion, a trial of quinidine is indicated in all cases of auricular fibrillation and mitral stenosis. Askey[64] commented that even when patients with mitral stenosis and auricular fibrillation are progressing satisfactorily with digitalis, such patients do even better with a regular rhythm after conversion with quinidine.

It is common experience that many patients with mitral stenosis, previously in regular rhythm, do not regain satisfactory cardiac competence or exercise tolerance as long as auricular fibrillation persists. Kerkhof and Baumann[39] demonstrated a 25 per cent increase in cardiac output in patients with mitral stenosis following conversion to regular rhythm. In some patients with mitral stenosis who have been in chronic failure with repeated emboli while fibrillating, we have noted striking clinical improvement after normal rhythm was re-established with quinidine.

These experiences indicate that although conversion with quinidine may be less successful and possibly more toxic in patients with mitral stenosis, worthwhile and, at times, spectacular results may follow conversion. In some instances, conversion of auricular fibrillation with mitral stenosis occurs after modest doses of quinidine in patients with relatively low blood levels, even though in other instances large doses and high blood levels are necessary. We believe a trial of quinidine is indicated in all patients with mitral stenosis in whom the clinical course has abruptly become worse with the appearance of auricular fibrillation and in whom cardiac failure cannot be adequately treated as long as the arrhythmia persists. In a few cases when mitral commissurotomy was performed in patients who had auricular fibrillation, to my knowledge none showed a reversion to normal rhythm as a result of the operation, but our experience with this procedure is limited. The problem of maintaining sinus rhythm is more difficult in patients with mitral stenosis than in patients who do not have a large, dilated left auricle, but, as will be discussed later, the percentage of successful maintenance is significant, provided adequate doses of quinidine are used. In the literature, the figures given for early relapse are too high, for the reason that the dose of quinidine usually recommended for maintenance (0.2 Gm. three times a day) is too low (see below).

Auricular fibrillation during thyrotoxicosis has been reported to be a contraindication to treatment with quinidine until after thyroidectomy has been performed (Parkinson and Campbell[1]). McMillan and Welfare[18] were unable to accomplish conversion in any of their patients with auricular fibrillation associated with thyrotoxicosis. Wilson and Wishart[48] produced sinus rhythm on four occasions in a patient with toxic goiter who received doses of 0.2 Gm. of quinidine intravenously. In our experience, conversion was obtained in several patients with thyrotoxicosis by inadvertence, either because the thyrotoxicosis was not recognized or because quinidine was given to suppress ventricular premature beats and auricular fibrillation unexpectedly reverted to sinus rhythm. In these patients, auricular fibrillation had existed for several weeks and probably was not the transient, acute variety of arrhythmia. None of the patients had severe, obvious hyperthyroidism. Goldman[19] had one similar case. Our experience is too limited to allow serious questioning of the time-honored position, but it may be pointed out that evidence supporting the viewpoint that quinidine should not be given to patients with auricular fibrillation in thyrotoxicosis is not abundant.

A similar problem exists with regard to the occurrence of auricular fibrillation during the course of rheumatic fever. We have had no experience with this combination, and in the classic work of Parkinson and Campbell[1] treatment of only one patient with auricular fibrillation and rheumatic fever was discussed. In this patient, vomiting, collapse, and rapid increase in size of the liver occurred after three doses of 0.3 Gm. of quinidine. The patient presumably did not receive digitalis before administration of quinidine, and the failure may have been due to the development of a rapid ventricular rate. Insufficient data were given to permit further comment.

Currently, an answer to the question posed at the beginning of the section seems to be as follows: The conditions which would respond most favorably to quinidine, and those in which its use would be least opposed by cardiologists, are: (1) auricular fibrillation persisting two weeks after thyroidectomy for thyrotoxicosis; (2) auricular fibrillation in patients with minimal or no enlargement of the heart and minimal or no cardiac failure, when the arrhythmia results in disturbing palpitations or dyspnea on effort and cannot be adequately controlled with digitalis (especially if the arrhythmia is of short duration); and (3) chronic auricular fibrillation in an individual with an otherwise normal heart. Some dissenters would not include this last condition, but the data presented by Phillips and Levine[37] are quite convincing. The three situations listed are considered the most favorable by most observers. In addition, however, recent authors[19,21,38,58,59,62,64] believe that conversion usually should be attempted in the following conditions: (1) chronic auricular fibrillation associated with embolic accidents; (2) auricular fibrillation when it complicates mitral stenosis and is associated with a sharp decrease in cardiac competence and when the "prefibrillatory" status is not restored by the usual therapeutic program; and (3) auricular fibrillation when it is present in a "cardiac cripple" and when, despite salt restriction, frequent injections of mercury, use of digitalis, and bed rest, the patient is still an invalid or is unable to work. In these patients, the maximum degree of cardiac competence should be obtained before treatment with quinidine is instituted.

The greatest disagreement among cardiologists, however, concerns the following clinical condition: chronic auricular fibrillation in patients with cardiac disease (especially in the elderly and when associated with mitral stenosis) when the patients are completely asymptomatic on treatment with digitalis alone. In this instance, the main purpose of conversion would be to prevent future emboli, since it has been shown that the cardiac output will not be increased after conversion if no cardiac failure was present before conversion and since Phillips and Levine[37] have demonstrated that cardiac failure is unlikely to appear for the first time if auricular fibrillation has been present for a year. Most cardiologists would not treat these patients with quinidine unless progressive cardiac difficulties developed. Askey[64] and Fahr[38] prefer to attempt to convert patients in this category who have mitral stenosis.

XV. RELAPSES

One of the most important problems in the treatment of chronic auricular fibrillation with quinidine is the prevention of relapses once sinus rhythm has been re-established. Parkinson and Campbell[1] indicated that sinus rhythm was maintained for a year or so in 52 per cent of their patients. The eleven patients in their series who had relapses, however, either had taken no quinidine for maintenance or had stopped it recently. McMillan and Welfare[18] found that the rhythm remained regular up to two years in 56.8 per cent of their patients and that of those in whom regular rhythm was maintained four months after conversion, 71.4 per cent had rheumatic heart disease. Fahr[38] stated that no relapses occurred when patients continued to receive adequate maintenance doses

of quinidine. Harris[65] followed twenty-six patients after conversion to normal rhythm who had not received maintenance doses of quinidine; fibrillation recurred in nine in a month, in sixteen in a year, and in twenty-four in two years. In our experience, the rate of relapse is closer to 20 per cent. In most cases in our series, the relapses occurred within two weeks of conversion and were usually due to inadequate dosage or failure of the patient to take the drug. McMillan and Welfare[18] also noted prompt relapse when quinidine was stopped.

In our earlier work, 0.2 Gm. three times a day was recommended as a maintenance dose, but this amount was soon found inadequate for many patients. We now use 0.4 Gm. three or four times daily after sinus rhythm has been restored, unless very large doses were required for conversion or unless low blood levels had resulted with ordinary dosage. Approximately 90 per cent of patients will be maintained satisfactorily for a period of months on a dose of 0.4 Gm. four times a day. If conversion required 4 to 6 Gm. of quinidine a day, a dosage of 0.6 Gm. four times a day can be used for the first two weeks, then decreased to 0.4 Gm. three times daily, to achieve midday blood levels of around 4 to 5 mg. per liter. McMillan and Welfare,[18] in a series of thirty-five patients, found the average amount required for conversion was 0.45 Gm. every four hours, and the average dose required for maintenance was 0.28 Gm. every six hours. Not all patients require continued administration of quinidine; in some individuals relapses may not occur after sinus rhythm has been restored even if the drug is stopped. This cannot be predicted, and it is better to give quinidine than to risk recurrence of the fibrillation, particularly since the arrhythmia will recur in most patients if maintenance doses are stopped.

Relapse is not entirely a matter of an adequate maintenance dose of quinidine. Progressive cardiac disease, severe emotional stress, or intercurrent illness may result in recurrence of auricular fibrillation, just as it may result in paroxysmal arrhythmias (see below) in patients who have been free of attacks for many months. After conversion has been finally achieved, such recurrences are discouraging, as in the case of a patient who had previously had a cerebral embolus and in whom fibrillation recurred as a result of strenuous vomiting following treatment with colchicine for acute gout.

The optimum length of time treatment with quinidine should be continued is not known. A number of our patients have taken 1.6 Gm. of quinidine daily for several years without toxicity and have remained in sinus rhythm. In patients without obvious heart disease, it may be possible to stop quinidine after regular rhythm has been maintained for a month. If relapse occurs, reconversion should be effected and maintenance doses of quinidine continued indefinitely. In patients with mitral stenosis or other significant cardiac disease, maintenance therapy should be continued indefinitely, since the conditions (large left auricle under increased pressure) leading to auricular fibrillation are still present and refibrillation would probably soon ensue.

XVI. PARENTERAL ADMINISTRATION OF QUINIDINE

Under most circumstances, oral doses of quinidine will suffice for conversion of either acute or chronic arrhythmia. Occasionally, because of the urgency of

the situation or because of vomiting or inability to take medication by mouth, as in postoperative states, coma, and similar situations, it is necessary to administer the drug parenterally. Quinidine can be given either intramuscularly or intravenously; the latter route is reserved for the most urgent situations (see below).

A number of preparations are available for intramuscular injection: (a) 15 per cent quinidine in urea-antipyrine,[66] (b) 20 per cent quinidine in propylene glycol,[51,67] and (c) 8 per cent quinidine gluconate (0.8 Gm. in 10 c.c.) (Lilly).[51]* All three preparations are satisfactory, although the first two have the advantage of a small volume of diluent. The disadvantage of the first solution is that it contains 15 per cent antipyrine; if frequent doses of quinidine are required, the patient receives equivalent antipyrine, an amount which may aggravate the hypotensive effects of quinidine. Quinidine gluconate (Lilly) has proved satisfactory; its only disadvantage is the large volume (10 c.c.) required if frequent doses are needed. In an unpublished study, Sweet and the author[51] have found that the maximum concentration of quinidine occurred earlier (one hour) and the peak level was higher with single intramuscular doses of quinidine gluconate than with equivalent oral doses of quinidine sulfate or equivalent intramuscular doses of quinidine in urea-antipyrine or in propylene glycol. Intramuscular injections of the latter two preparations produced slightly higher levels, although not strikingly so, than oral doses of quinidine.

Intramuscular injection of quinidine has proved satisfactory in treating acute arrhythmias, although experience is as yet limited. In eight cases of acute tachycardia (auricular, nodal, or ventricular), conversion occurred within two hours after a single intramuscular dose of 0.8 Gm. of quinidine gluconate. In patients with ventricular or nodal tachycardia associated with serious symptoms or in instances where it is necessary to stop an arrhythmia promptly, repeated intramuscular injections of 0.8 Gm. of quinidine gluconate can be given at intervals of one to two hours. Experience with multiple intramuscular injections of quinidine is still limited. Careful observation for toxicity, as described in Section III, is essential. Hypotension is more likely to occur when quinidine is administered intramuscularly than when it is given orally, but the drug may be used even if the blood pressure is low as a result of the arrhythmia. Severe hypotension may actually be an indication for the intramuscular route, since the attack may be stopped more quickly if this method of administration is used. If the situation is less urgent and if the ventricular tachycardia is not associated with serious symptoms, quinidine can be given orally in doses of 0.4 to 0.6 Gm. every two hours for five doses, as described for auricular fibrillation, with an increase in amount if the ventricular tachycardia persists.

Intravenous administration of quinidine should be reserved for the most urgent cases, when the situation is such that cessation of the tachycardia is advisable in minutes to an hour. Wilson and Wishart[48] gave 0.2 Gm. of quinidine in 25 c.c. of solution to thirty patients with auricular fibrillation or flutter. In one patient who received 0.4 Gm., ventricular flutter occurred and death resulted

*We are grateful to Dr. Kenneth Kohlstaedt of Eli Lilly and Company, Indianapolis, Ind., for generous supplies of both quinidine gluconate and quinidine in propylene glycol.

in two or three minutes. Hepburn and Rykert[68] demonstrated that ordinary quinidine sulfate could be dissolved in saline or glucose (3.3 Gm. in 500 c.c. of solution) and given by slow infusion at the rate of 1 to 2 c.c. a minute. This technique has proved effective and relatively safe in the few instances in which we have used it. In our experience, small doses of quinidine given intravenously may stop ventricular tachycardia, whereas large doses given orally may not. Quinidine by the intravenous route results in high blood levels within a few minutes; the peak levels begin to subside in five to ten minutes. Anesthesia may permit intravenous quinidine to be given more safely; this may explain why Collins[69] was able to give quinidine intravenously without difficulty to twenty-five patients who developed arrhythmias during operation. He stated that reversion to sinus rhythm occurred in all twenty-five patients in about five minutes of the injection. No details were given as to whether electrocardiographic changes resulted from the intravenously administered quinidine.

Quinidine gluconate can be given intravenously, either undiluted or, preferably, diluted to 50 or 100 c.c. in saline or glucose solution, and injected slowly, with frequent blood pressure determinations and continuous electrocardiograms during the administration. Recently, in a patient critically ill with ventricular tachycardia following a myocardial infarction, conversion failed to occur after oral administration of 2.4 Gm. of quinidine sulfate in four hours. The blood level was 6 mg. per liter. Conversion resulted thirty-five minutes after 0.3 Gm. of quinidine was given intravenously, at a blood level of 11 mg. per liter. Several other acute and severe arrhythmias have been successfully converted with quinidine by the intravenous route and at comparable blood concentrations. In one patient with chronic auricular fibrillation (treated by Dr. John Carbone and Dr. William Ashley at the San Francisco Hospital), slow intravenous administration of quinidine gluconate (0.8 Gm. in 50 c.c. of 5 per cent dextrose) resulted in conversion within several hours. Hypotension and short runs of ventricular premature beats occurred when the infusion was given at a rate of 2.2 c.c. a minute, but not when the rate of administration was 1 or 1.5 c.c. a minute. Armbrust and Levine,[70] Herrmann and Hejtmancik,[71] Chapman,[72] and Clagett[73] have reported experiences with quinidine administered intravenously to patients with ventricular tachycardia. That quinidine by the intravenous route is not innocuous and that the drug probably should not be given by this route if it can be given orally or intramuscularly are clear from the article by Acierno and Gubner.[74] These investigators noted four deaths in forty-four patients with cardiac arrhythmias who had received intravenous injections of quinidine. The deaths in their series, as in those of Armbrust and Levine,[70] all occurred in patients with organic heart disease who were in shock or had congestive failure.

If intravenous administration of quinidine is indicated, it would appear then that the technique of Hepburn and Rykert[68] should be used or that quinidine gluconate (0.8 Gm. dissolved in 50 to 100 c.c. of solution) should be given at a rate of 1 c.c. a minute for maximum safety. Clagett[73] did not encounter serious toxicity in thirteen patients receiving thirty doses of quinidine lactate* intra-

*This Lilly preparation is no longer marketed and has been superseded by quinidine gluconate.

venously. He attributed the absence of toxicity to dilution (0.65 Gm. or 10 c.c. diluted to 50 c.c.), slow administration (not exceeding 2 c.c. a minute), and constant observation while the drug was being given.

XVII. PREVENTIVE AND PROPHYLACTIC USES OF QUINIDINE

A variety of patients with and without heart disease have acute paroxysmal arrhythmias: auricular tachycardia, auricular flutter, auricular fibrillation, nodal tachycardia, or ventricular tachycardia. These paroxysmal arrhythmias may occur at rare or infrequent intervals, such as once a year, or they may occur at frequent intervals, such as several times a day, week, or month. When they occur, the patient may be unaware of the change in rhythm, may have mild symptoms of faintness, dizziness, and palpitation, or may develop in minutes, hours, or days clinical states rapidly growing worse, with development of cardiac failure, coronary insufficiency, and/or shock. The latter three conditions are not apt to occur unless serious cardiac disease is present prior to the arrhythmia.

In some patients, coronary insufficiency of a high degree may occur if the ventricular rate is sufficiently rapid or if the attack is prolonged over a period of hours. In patients with significant symptoms or signs resulting from frequently recurring arrhythmias, it is highly desirable to prevent recurrence of the attacks. Digitalization and maintenance therapy may be helpful in preventing certain cases of paroxysmal auricular rhythms, but are only rarely of aid in nodal or ventricular rhythms. In our experience, both auricular and ventricular arrhythmias, as well as nodal recurrent paroxysmal arrhythmias, may be prevented successfully with adequate oral doses of quinidine, although, as will be described later, under special circumstances arrhythmias may break through the quinidine barrier. The usually recommended dose of 0.2 Gm. three times a day was found to be inadequate in preventing many cases of recurrent arrhythmia, but is adequate in some; we have found 0.4 Gm. three or four times a day the average adequate dose. These doses produce a midday blood quinidine level of 3 to 5 mg. per liter, with morning (8 A.M.) levels 1 to 2 mg. per liter lower and bedtime levels 1 to 2 mg. per liter higher. In some patients, usually those in whom the blood concentration is low on 1.6 Gm. of quinidine a day, it may be necessary to increase the dose to as high as 3.2 to 3.8 Gm. a day. The latter amount was used in a patient with paroxysmal ventricular tachycardia in whom the blood level was only 5 to 6 mg. per liter despite this high dose. In one patient who had recurrent paroxysmal auricular fibrillation for twelve years, a number of different physicians were unsuccessful in preventing attacks because not one of them prescribed a dose in excess of 0.4 Gm. three times a day. In the same patient, we found that 0.4 Gm. taken five or six times a day or 0.6 Gm. three or four times a day and attainment of a blood level of 4.3 mg. per liter were required for prevention. Whereas this patient had had attacks several times a week for twelve years, he became free of them for many months on a dosage of 2.4 Gm. of quinidine a day. As a rule, patients who require relatively large doses of quinidine (more than 1.6 Gm. a day) have relatively low blood levels on such amounts. In our experience, a satisfactory blood concentration for prevention of recurrent arrhythmias is somewhat lower than that required for conversion of established arrhythmias, i.e., in the neighborhood of 4 to 5 mg. per liter.

As described in the section on the methods of administering quinidine, any fixed schedule of dosage achieves peak blood levels in two to four days; for example, if doses of 0.2 Gm. three times a day fail to prevent attacks, continuing with the same amount for more than a few days is futile. The dose must be increased to 0.4 Gm. three times a day, and if this proves inadequate after three or four days, a greater number of doses must be given in a day (e.g., 0.4 Gm. four to six times a day) or the size of the individual dose must be increased (e.g., 0.6 Gm. three times a day). In this manner, but guided by the frequency of the paroxysmal attacks of arrhythmia and the tolerance of the patient, the dose is progressively increased until a dose schedule and blood level are achieved which successfully prevent the attacks or which result in toxic effects that preclude further treatment. In our series of fifty cases,[59] 3.8 Gm. during the day have been the largest dose required, although not all patients could tolerate the dose required because of nausea, vomiting, or diarrhea. In patients who developed diarrhea or nausea, the dose was decreased to the maximum amount tolerated; this often decreased the frequency and severity of the attacks, if insufficient to prevent them entirely. The total daily dose is more important than the total amount of quinidine given over a period of a month, since if 2.0 Gm. a day for three to five days are unsuccessful, 60 Gm. in thirty days will not be less so, whereas 3.0 Gm. a day may be successful in preventing the arrhythmia. Gold[4] also has emphasized this point and, on clinical grounds, concluded that cumulation ceases after three or four days. In our data on daily blood concentrations on fixed daily doses, we have found this to be true, although at times cumulation may persist for four to six days or at other times last only two days. When quinidine is given more frequently, such as every two hours, cumulation decreases after the third dose and usually ceases after the fifth or sixth dose.

Prophylactically, quinidine may be used to prevent significant arrhythmias (a) following myocardial infarction, (b) in patients undergoing major surgical procedures, especially pulmonary operations, and (c) in any situation where the incidence of arrhythmia may be expected to be increased. In our experience, a safe and effective dose is 0.4 Gm. three or four times a day. On the latter dose, we have observed no serious arrhythmias in patients for a year following myocardial infarction or pulmonary operation,[51] although the high incidence of arrhythmias under these circumstances is well known. Work is continuing on the prophylactic use of quinidine; since the data at the present time are limited, it is probable that in some cases this average dose may have to be altered.

Toxicity resulting from the average preventive dose of 0.4 Gm. four times a day is extremely rare. Important electrocardiographic changes and hypotension occur infrequently. Nausea and diarrhea occasionally occur, but seldom are severe enough to preclude use of quinidine. In an incomplete, unpublished study on a series of patients with acute myocardial infarction,[51] administration of 0.4 Gm. four times a day resulted in only one toxic reaction; left bundle branch block with a QRS complex of 0.16 second developed in a patient who had an incomplete left bundle branch block with a QRS complex of 0.13 second before administration of quinidine.

Prophylactic or preventive uses of quinidine provide only a relative brake on the appearance of an arrhythmia. If the clinical condition is sufficiently severe, if cardiac failure or progressive coronary failure develops, or if significant emotional crises appear, an acute arrhythmia may break through the protective curtain or barrier of quinidine. The effect of emotional strain has impressed us as most important; we have seen an arrhythmia develop promptly as a result of acute emotional stress in patients who had been free of attacks for months while under treatment with quinidine. For instance, one patient developed auricular tachycardia as soon as she saw her husband come home intoxicated; a second patient developed auricular fibrillation when told he needed an operation; a third, whose wife had been operated upon for a cataract, developed ventricular tachycardia when he discovered that she was unable to see after her bandages were removed. Many other examples could be cited. It is interesting that in each instance the patient developed the identical arrhythmia of the attacks he had recurrently before treatment with quinidine. The relationship between emotional stress and the type of cardiac arrhythmia has been discussed recently by Altschule,[75] Katz and associates,[76] and Duncan and associates.[77] It is difficult to anticipate some of the emotional crises, although we were successful in one case, a woman who developed paroxysmal auricular tachycardia about 6:30 in the evening every time she gave an important dinner party.

XVIII. SUMMARY AND CONCLUSIONS

It is apparent from what has been written that quinidine is a valuable drug for the prevention and treatment of the cardiac arrhythmias. Its value is dimmed somewhat by its toxicity, which is usually mild and relatively unimportant but which occasionally may be serious, although rarely fatal. The toxicity can be minimized by careful precautions, including frequent clinical and electrocardiographic observations during administration of the drug.

Measurement of the concentration of quinidine in the blood, which recent methods have made feasible, has clarified our knowledge of its clinical pharmacology and has been of definite help in aiding the physician to plan and carry out adequate therapy. When the blood concentration is less than 6 mg. per liter, the drug usually can be continued or increased with relative safety, provided no evidence of toxicity is present. Considerable caution should be exercised if the blood concentration exceeds 9 to 10 mg. per liter.

The physician utilizing quinidine should become skilled in its use, aware of its hazards, and also aware of its beneficial effects. As Sir Thomas Lewis[14] remarked in an early classic paper, "When in a case of auricular fibrillation the normal rhythm is restored, the gain to the patient is considerable." The physician should be prepared to attempt conversion of chronic auricular fibrillation by the use of quinidine whenever, despite other forms of treatment, the patient is invalided, particularly if his disability is the result of the arrhythmia, as in some patients with mitral stenosis. The risk of the disease should be weighed against the risk of the treatment, and, if the former is great, the risk should be taken honestly. The calculated risk is justified whenever, in the physician's opinion, significant benefit may be derived from restoration of normal rhythm.

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Book Reviews

CONGENITAL HEART DISEASE. By J. W. Brown, M.D. (Lond.), F.R.C.P. Second Edition. London and New York, 1950, Staples Press, 344 pages with 128 figures.

This monograph may best be described as a comprehensive summary of the literature on congenital heart disease up to and including 1948, based on a foundation of the author's extensive personal experience. It is written in a particularly lucid manner. Historians will be pleased with the complete way in which the earliest references and the rarest anomalies have been covered. The arrangement follows for the most part Maude Abbott's classification. Presentation of embryological and developmental fact and theory is particularly good.

The book's readability will recommend it to the general physician who wishes to acquire a solid background against which to view a special branch of cardiology which is rapidly developing. But rapid growth of the subject matter means also that, by the time a book such as this appears in print, some important material is already out of date. Simple clinical and radiologic diagnosis is well covered, but the cardiologist who is looking for detailed information on angiocardiography and cardiac catheterization will not find it. Electrocardiography is limited to the three standard leads. Discussion of treatment on the whole is sound, although most will agree that the urgency about operating on an infected ductus arteriosus has now been removed by antibiotics.

A full bibliography is included; for many readers its value would have been enhanced by including the title of each article. The book is beautifully produced and well illustrated.

J.P.

HERZSCHALLDIAGNOSTIK IN KLINIK UND PRAXIS. By J. Schmidt-Voigt, M.D. Stuttgart, 1951, Georg Thieme Verlag, paper bound, 116 pages.

This small monograph is planned as a simple introduction into the practical and diagnostic significance of heart sound recordings. The book is written in easily readable German. It serves as a guide to the newcomer in this field and is a handy reference for the more experienced worker as to the significance, analysis, and interpretation of phonocardiograms. This objective visual method is useful for checking subjective impressions of auscultatory findings. Phonocardiography is probably a valuable method to be carried out in the clinic, but it has been largely neglected in the United States.

The book covers a subject quite completely yet succinctly and in logical order. Beginning with the physical and physiological bases, it points out the limits of auscultation, describing the techniques and the apparatus and actual records of the normal heart sounds, the murmurs in general, extracardiac and intracardiac, systolic and diastolic, singly and in combinations, musical murmur, heart tones, systolic and diastolic gallop rhythms, changes in intensity of the heart sounds, intensification, and diminution of sounds. It dwells upon the significance of phonocardiographic findings in cardiac diagnostic procedure.

It is true that stethocardiographic equipment is available in portable form along with the electrocardiographic recording apparatus. Internists in general have neglected this field, and it is feared that few will do otherwise. Those who can read scientific German will find that this book offers a practical guide for rounding out their cardiovascular diagnostic armamentarium. The reproductions are not as good as might be desired, yet the book is recommended. It should be of value not only to cardiologists, but also to the general internist.

G.H.

DIE UNTERSUCHUNG UND BEURTEILUNG DER RÖNTGENOLOGISCHEN HERZGRÖSSE. By Rautmann, H. Dietrich Steinkopf Verlag, Darmstadt, 1951, 146 pages with 27 figures.

This is the ninth volume of the series, "Kreislauf-Bücherei," sponsored by the German Society for the Study of the Circulation (deutschen Gesellschaft für Kreislaufforschung). Like its predecessors, this volume is apparently addressed to the serious but not necessarily expert or scholarly German physician. His counterpart in the United States will find only small interest or value in the present volume. The author is a professor of internal medicine whose interest in the size of the heart was an outgrowth of his early interest in norms and the question of variability, an interest which found expression in a number of studies on the hearts of athletes in the late twenties and early thirties. The book faithfully reflects all this with a minimum of attention to more recent physiological and technological developments. There are almost no references to non-German publications. The German papers on athlete's heart, which has been a favorite subject of the author for many years, are reviewed at length, but some of the more critical German-language analyses of the general problem of heart size estimation, notably those of Benedetti (cf., e.g., Ergebn. d. inn. Med. u. Kinderh. **51**:531, 1936) and Ludwig (cf., Fortschr. a. d. Geb. d. Röntgenstrahlen **59**:1, 250, 1939), are less adequately treated. Emphasis throughout is on the transverse and long diameters of the heart, with little or no attention to projection area, volume, cardiac output, or function as related to heart size. There is no real analysis of the problems of consistency, reliability, and predictive value of measurements. Statistical concepts are introduced in the book in several places, together with very elementary expositions of variability and regression, but these are likely neither to instruct the uninitiated nor to impress the critical scientist. The author concludes that cardiac health may not be judged from heart size alone and that absolute norms for the roentgenological heart size are unattainable except in the sense that perhaps the frequency of occurrence of particular heart sizes in healthy people may be specified. That these should emerge as major conclusions near the end of the treatise is, perhaps, an indication that the viewpoint of the book is not as recent as is indicated by the publication date of 1951.

A.K.

HYPERTENSION. A symposium edited by E. T. Bell, M.D. Minneapolis, 1951, University of Minnesota Press.

The proceedings of a symposium on hypertension which was held at the University of Minnesota in the fall of 1950 in honor of Dr. Elexious T. Bell, Dr. Benjamin J. Clawson, and Dr. George E. Fahr are presented in this volume. A series of thirty papers by twenty-four authors covers the experimental, clinical, and therapeutic aspects of hypertension.

Of special interest was the paper of Dr. Arthur Grollman, who demonstrated the development of hypertension in dogs subjected to bilateral nephrectomy and maintained by peritoneal lavage. This contribution establishes the fact that hypertension may occur in the absence of kidney tissue. A divergent viewpoint, namely, that the presence of kidney tissue with decreased renal blood flow leads to the development of high blood pressure, was presented by Dr. Harry Goldblatt. The renin-angiotonin pressor system was also reviewed by Dr. Irvine Page. This book presents an excellent summary of numerous aspects of a disease of which the final elucidation of the causative mechanism is still in doubt.

H. E. H.

CLINICAL UNIPOLAR ELECTROCARDIOGRAPHY. By B. S. Lipman, M.D., and E. Massie, M.D. Chicago, 1951, The Year Book Publishers, Inc., 232 pages. Price $5.00.

In reading or studying this book, the student readily slips into the mood of sitting, as one of a small group, listening to an explanation of unipolar leads by an able teacher who stands before a blackboard on which he makes good drawings to clarify what he describes. The teacher is good because he moves from one step to another at the student's pace, and, if a point is not yet clear after the first rendition, this can be read again and again; the teacher seems to stop and repeat more slowly. The excellent drawings which are woven into the text make for this impression and

distinguish this from other books which have the same general purpose. The authors have drawn liberally on their own experience in learning and in teaching to create as good a substitute for lectures and seminars as this reviewer has seen.

The first 150 pages are devoted to the text, and there are sixty-three pages of illustrative electrocardiograms. This book will be found very satisfactory, not only by the undergraduate student, but also by the experienced cardiologist, who has the task of reading meaning out of and into electrocardiographic patterns and that of making more precise calculations based on the concepts of unipolar leads. It is a good book on the grammar of the newer language of electrocardiography. The authors wisely sustain uniformity and continuity by the use of diagrams throughout the text, and the set of illustrative electrocardiograms at the end is analogous to a glossary in a grammar book. The size and format of the book are convenient and attractive.

H. S.

CHIRURGIE DU COEUR. F. d'Allaines and collaborators. Paris, 1950, L'Expansion Scientifique Française, 350 pages. Price 1,200 francs.

This monograph is a report of the first two and one-half years' work in cardiac surgery as done in France at the Broussais Hospital in Paris.

It is well written, but is necessarily somewhat repetitive in that many collaborators review the same problems.

A full account is given of the team's experience in (a) congenital heart disease and (b) acquired heart conditions.

Four lengthy chapters (out of twelve) are devoted to the azygos-pulmonary vein shunt in mitral stenosis and the ligature of the inferior vena cava in decompensation. These procedures are now more of historical than practical interest because of more recent successful surgical attacks on the valves themselves.

The illustrations are not of very high standard though legible. The photomicrographs are poor.

One has the impression that the book is a collection of papers and that the editor could have shortened the monograph considerably.

If one wishes to have an insight into what one French surgical team has accomplished, starting late and under great difficulties, the book is worth reading.

E. D. G.

Erratum

On page 114 of the July, 1951, issue in the article "The Patient With Functional Cardiovascular Disorders (Neurocirculatory Asthenia)" by Lieutenant Colonel Weldon J. Walker, references 30 and 31 should read as follows:

30. Hanson, F. R.: The Factor of Fatigue in the Neuroses of Combat, Bull. U. S. Army M. Dept., Supp. Issue, **9**:147-150, 1949.

31. Hanson, F. R., and Ranson, S. W.: Statistical Studies, Bull. U. S. Army M. Dept., Supp. Issue, **9**:191-204, 1949.